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Enantioselective Copper-Catalysed Reductive Coupling of Alkenylazaarenes

Thesis Submitted in Accordance with the Requirement of the University of
Edinburgh for the Degree of Doctor of Philosophy

By

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August 2015

DECLARATION

I hereby declare that, except where specific reference is made to other sources, the work contained within this thesis is the original work of my own research since the registration of the PhD degree in September 2011, and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification.

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The following chapters contain results reported in the following publications:

Chapter 2 – Enantioselective Copper-Catalysed Reductive Coupling of Alkenylazaarenes with Ketones; Saxena, A.; Choi, B.; Lam, H. W. *J. Am. Chem. Soc.* **2012**, *134*, 8428-8431. **DOI:** 10.1021/ja3036916

Chapter 3 – Enantioselective Copper-Catalysed Reductive Coupling of Vinylazaarenes with *N*-Boc Aldimines; Choi, B.; Saxena, A.; Smith, J. J.; Churchill, G. H.; Lam, H. W. *Synlett* **2015**, *26*, 350-351. **DOI:** 10.1055/s-0034-1379548

Signed

Bonnie Choi

For Chris

ACKNOWLEDGEMENTS

First, I would like to thank my supervisor Professor Hon Wai Lam for the opportunity to undertake research within his group. Most of all, I thank him for his patience in teaching, his support and continuous guidance throughout the course of my postgraduate studies. Without him this work would not have been possible, and I am grateful for everything he has taught me throughout my PhD and I hope to take all that I have learned with me from this chapter, and onto the next chapter of my career.

Thank you to AstraZeneca and the University of Edinburgh for providing funding and facilities for my PhD research. Thank you to Dr Gwydion Churchill for being my CASE supervisor and for everyone who made me feel welcome during my industrial placement at Macclesfield.

I would like to thank the staff at the School of Chemistry from the University of Edinburgh and from the University of Nottingham for all the help and support they have provided over the years.

I would like to thank all past and present members of the Lam group that I have had the opportunity and privilege to work with. You have all contributed to providing a great and memorable experience for me over the course of my PhD. To the post-docs; Dr Graham Pattison, Dr Alan Burns, Dr Dan Best, Dr Suresh Chidipudi, Dr Yunfei Luo, Dr David Burns, Dr Ben Partridge, Dr Jose Martínez, Dr Lucia Saya and Dr Celia Incerti-Pradillos, thank you for being so approachable and helping me with any issues that I had. It has been a pleasure to work with and learn from you. Special thanks to Dr Alan Burns, Dr Dan Best and Dr Jose Martínez for their time, patience and effort in proof-reading this thesis. I am very grateful and your contributions are fully appreciated.

To all the students in the Lam group it has been a pleasure getting to know each and everyone of you and thank you for creating a fun and friendly working environment. Aakarsh Saxena is especially thanked for showing me the ropes when I first started,

for his patience and continuous guidance and all the work that has led to our publications on the Enantioselective Copper-Catalysed Reductive Coupling of Alkenylazaarenes. Hamish, Jorge, Szymon, Josh, Amael and Imtiaz-Nottingham wouldn't have been half as much fun without you guys. I hold many fond memories of "Classic Choi" moments with you guys. Special thanks to Imtiaz for proof-reading as well! To Sam, Charlene, Donna, Martin, Alain, Iain, Darryl, Sit, Alison, Boris, Jen and Jonathon, it was great getting to know and work with you in Edinburgh.

I would also like to thank all my friends and family, near and far, for all their support and encouragement over the years and for always believing in me. Special thanks to Ashton, Fran, Jenni, Sam, Hanne, Catherine, Sarah, Sara and Nic for putting up with all the time I have spent talking about my thesis!

Most importantly, I would like to thank my parents for their unconditional love and continued support. Thank you for always encouraging me to take on new and exciting opportunities and to continuously challenge myself, which has allowed me to get to where I am today. Thank you also for always standing by me and supporting my decisions.

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LIST OF ABBREVIATIONS

δ	delta
μw	microwave
Ac	acetyl
acac	acetylacetonate
app	apparent
aq.	aqueous
Ar	aryl
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	<i>t</i> -butyloxycarbonyl
br	broad
<i>c</i>	concentration
<i>ca.</i>	circa
cald	calculated
cat.	catalyst
cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
CuH	copper hydride
Cy	cyclohexane
d	doublet
DBM	dibenzoylmethane
DCM	dichloromethane
DEMS	diethoxymethylsilane

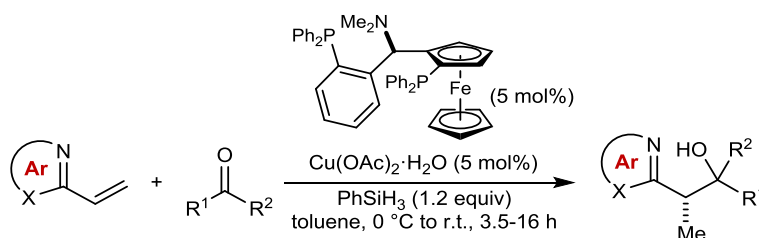
DEPT	distortionless enhancement by polarisation transfer
DIBAL	diisobutylaluminium hydride
DIFLUORPHOS	5,5'-bis(diphenylphosphino)-2,2',2',2'-tetrafluoro-4,4'-bi-1,3-benzodioxole
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
<i>dr</i>	diastereomeric ratio
<i>ee</i>	enantiomeric excess
EI	electron impact
equiv	equivalents
ES	electrospray
ESI	electrospray ionisation
EVK	ethyl vinyl ketone
EWG	electron withdrawing group
FT	Fourier transform
Het	heterocycle
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
IR	infrared spectroscopy
IPA	<i>iso</i> -propyl alcohol
<i>i</i> -Pr	<i>iso</i> -propyl

L _n	ligand
m	multiplet
m.p.	melting point
MTBE	methyl <i>tert</i> -butyl ether
MVK	methyl vinyl ketone
NHC	<i>N</i> -heterocyclic carbene
NMR	Nuclear magnetic resonance
Nu	nucleophile
pin	pinacol
PMHS	polymethylhydrosiloxane
PMP	<i>p</i> -methoxyphenyl
Ph	phenyl
<i>q</i>	quartet
<i>rac</i>	<i>racemic</i>
rt	room temperature
<i>s</i>	singlet
<i>t</i>	triplet
<i>tert</i>	tertiary
TLC	thin layer chromatography
THF	tetrahydrofuran
TMDS	1,1,3,3-tetramethyldisiloxane
Ts	<i>p</i> -toluenesulfonyl
UV	ultraviolet spectroscopy

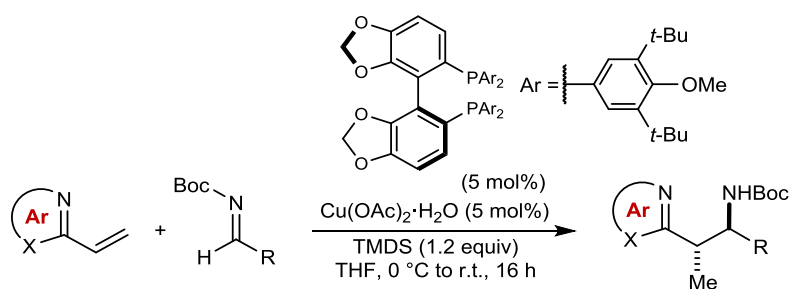
ABSTRACT

Chiral azaarene-containing molecules, tertiary alcohols and α -stereogenic amines are ubiquitous structures in pharmaceuticals, agrochemicals and natural products. The development of new catalytic enantioselective methods to construct molecules containing these chemotypes is of significant utility. Recent efforts within the Lam group have targeted the development of processes that exploit the embedded imine functionality within an azaarene to activate adjacent alkenes towards nucleophilic additions. Chapter 1 reviews the current state of the art with respect to nucleophilic additions of alkenylazaarenes and catalytic conjugate reduction reactions.

Chapter 2 describes a catalytic, enantioselective reductive coupling of 2-alkenylazaarenes with ketones using chiral CuH-bisphosphine complex in the presence of PhSiH_3 as a hydride source. The scope of this process is broad, with eleven different types of azaarenes and a range of acyclic and cyclic ketones demonstrated as effective coupling partners. β -Substitution on the alkene is tolerated, and the reactions proceed under mild conditions to deliver products with good to high levels of diastereo- and enantio- selection.



Chapter 3 describes, further investigation of the scope of enantioselective reductive coupling, using *N*-Boc aldimines as electrophiles. This process is tolerant of a variety of vinylazaarenes and *N*-Boc aldimines, and provides aromatic heterocycles bearing α -stereogenic amines with good to moderate yields and good to excellent levels of diastereo- and enantio- selection.



LAY SUMMARY

A catalyst is defined as a substance that can lower the energy barrier for a chemical reaction to proceed whilst remaining unchanged at the end of the reactions. Metal catalysts is a useful tool to enable chemical reactions to occur that would not take place under normal reaction conditions.

The use of a catalyst derived from the metal copper is a common theme throughout this thesis. Copper is cheap, and earth abundant metal developing new chemical transformations employing such a metal has economical and environmental advantages.

In this regard, a new chemical transformation has been developed employing a copper catalyst and is described in this thesis, which results in the creation of novel chemical compounds with motifs that are prevalent in many natural products. The development of such methodology have potential to provide easier access to building blocks for pharmaceuticals and other biologically active compounds.

1. ENANTIOSELECTIVE COPPER-CATALYSED REDUCTIVE COUPLING OF ALKENYLAZAARENES

1.1 Introduction

1.1.1 The Significance of Chirality

Chirality describes the symmetry property of a molecule that cannot be superimposed onto its mirror image. Derived from the Greek word for 'hand', the iconic conceptual illustration of chirality is the difference between our left and right hands. Despite having the same composition, hands are related as non-superimposable mirror images and are non-identical. This concept is of great importance at the molecular level where, just as a right hand will not fit a left glove or operate a pair of left handed scissors, the handedness of a chiral molecule can greatly affect its interactions with asymmetric biological environments.

Chirality has a very significant role in living organisms as numerous biological compounds are inherently chiral. Compounds such as DNA, proteins and carbohydrates are all chiral. To function properly they require highly precise interactions in which the host molecule interacts with two enantiomeric molecules in different ways. Enantiomers of a compound such as a drug can have vastly different effects on the body. For example, the non-steroidal anti-inflammatory drug Naproxen (**1**) is marketed as the (*S*)-enantiomer as it is 28 times more effective than the (*R*)-enantiomer.¹ For the drug Ibuprofen (**2**), the (*S*)-enantiomer is biologically active, however the inactive (*R*)-enantiomer racemises *in vivo* allowing the racemic drug to be administered (Figure 1.01).²

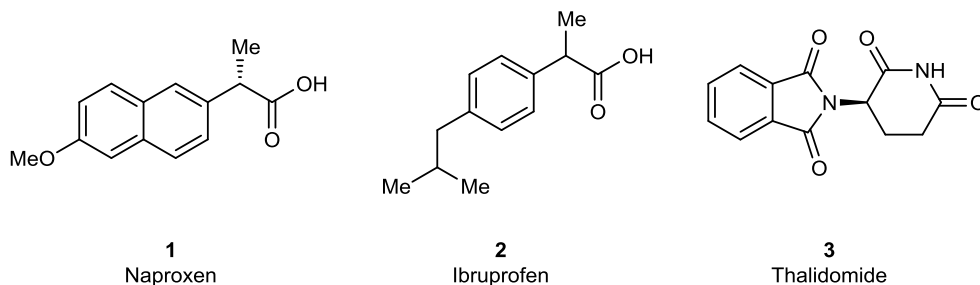


Figure 1.01: Chiral Drug Molecules

In certain cases one enantiomer produces a beneficial effect, while the other is associated with detrimental side-effects or lacks efficacy. Such was the case of the drug Thalidomide (**3**), prescribed in the 1960s to alleviate morning sickness in pregnant women. Tragically, women who were administered this drug bore children with limb deformities. Thalidomide was marketed as a racemate, where the (*R*)-enantiomer had desirable sedative properties while its (*S*)-enantiomer is teratogenic and induces fetal malformations.³ However, dosing with optically pure (*R*)-Thalidomide would still lead to (*S*)-Thalidomide in the body as the drug racemises *in vivo*. After the devastating effects of Thalidomide, in 1987 the U.S. Food and Drug Administration (FDA) published a set of guidelines, followed by a policy statement in 1992 discouraging the development of racemic drugs.⁴ The FDA now requires substantial analysis of both enantiomers of any new chiral drug.

In 2013, 8 out of the top 10 selling small molecule drugs worldwide were chiral, and 4 out of the top 10 selling drugs contained at least one nitrogen-containing aromatic heterocycle (azaarene); exemplifying azaarenes as key building blocks for drug discovery (Figure 1.02).⁵

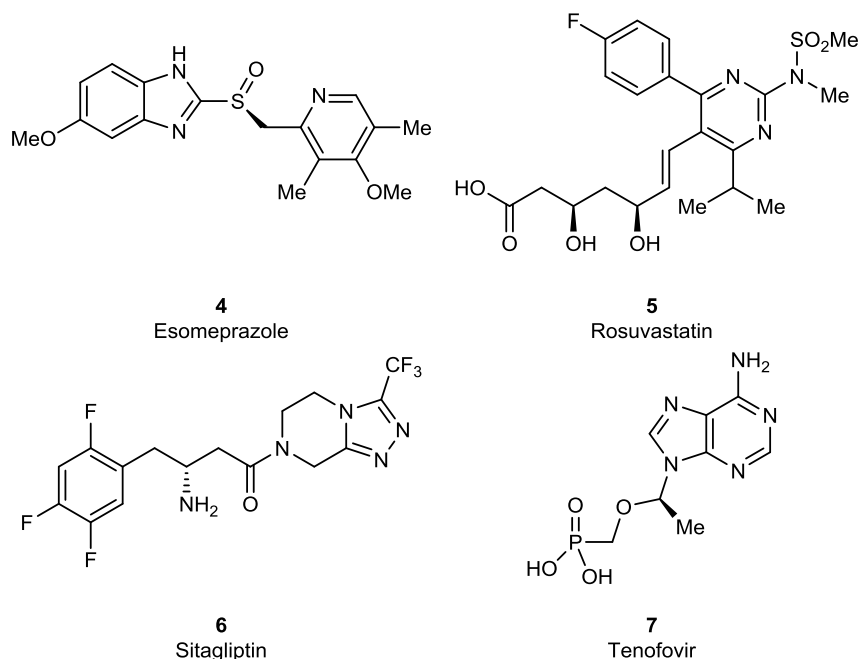


Figure 1.02: Examples of Azaarene-Containing Medicines

Additionally, azaarene motifs are prevalent in numerous natural products, agrochemicals and dyes; an example of each is illustrated in Figure 1.03.

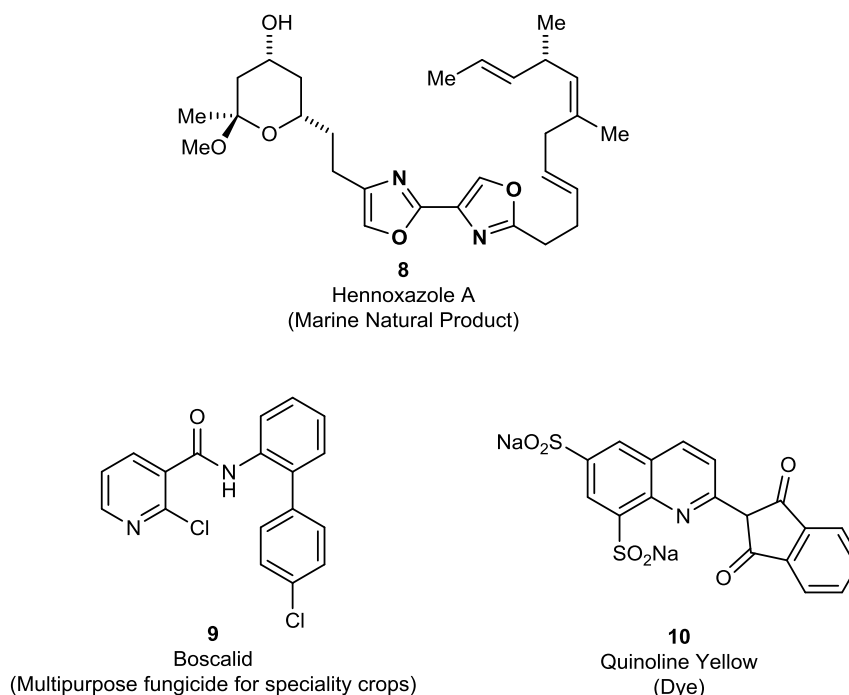


Figure 1.03: Examples of Azaarene-Containing Compounds

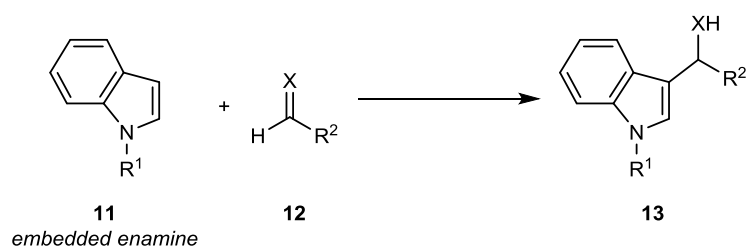
This highlights the importance of developing enantiopure materials, and that research into the functionalisation of chiral azaarenes and their derivatives is a valuable endeavor for the development of new pharmaceuticals and other synthetically useful compounds.

1.1.2 Alkenylazaarenes as Activating Groups

Currently, the principal methods for functionalisation of azaarenes are $\text{S}_{\text{N}}\text{Ar}$ reactions⁶ and metal-catalysed cross-coupling reactions.⁷ C-H bond activation has also become increasingly popular in recent years.⁸ However, these methods do not generally furnish chiral products. With azaarenes featuring prominently in chiral pharmaceuticals, natural products and agrochemicals, there is a huge drive to develop catalytic enantioselective methods to synthesise compounds incorporating this heterocyclic framework. There are existing methodologies for synthesising azaarene-

containing substrates where the azaarene acts as a non-participating by-stander; however, the development of methodology which takes advantage of the inherent chemical properties of the azaarene itself to promote the reaction should prove to be a potent and complementary tool for their synthesis.

An existing and well established class of reaction which fulfils this criterion is the catalytic enantioselective Friedel-Craft additions of π -excessive azaarenes to a π -electrophile (Scheme 1.01).⁹



Scheme 1.01: Friedel-Crafts Additions of π -Excessive Azaarenes to π -Electrophiles

This methodology relies on an embedded enamine within π -excessive azaarenes such as indoles or pyrroles which renders the azaarene nucleophilic. However, many classes of azaarenes do not contain an embedded enamine but rather an embedded imine (Figure 1.04).

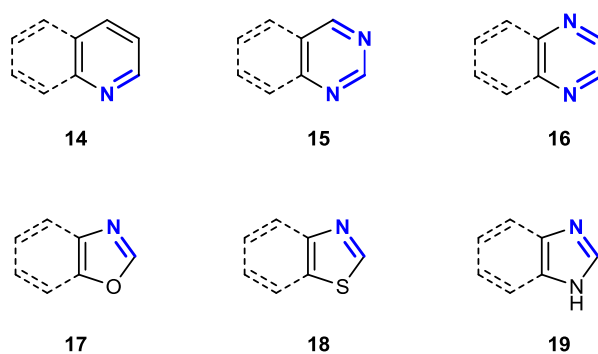
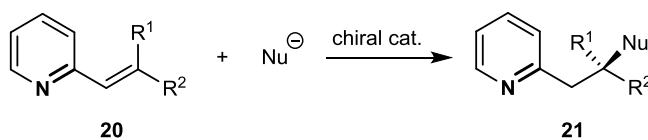


Figure 1.04: Azaarenes Containing an Embedded Imine

The embedded imine exhibits electron-withdrawing properties akin to those of carbonyl groups. This similarity raised questions as to whether the electron-withdrawing nature of the $C=N$ moiety can facilitate reactions that are normally

associated with carbonyl functionality. For example, could a prochiral alkenylazaarene such as 2-alkenylpyridine **20** be a feasible substrate for catalytic enantioselective 1,4 nucleophilic additions, where the embedded imine activates the adjacent olefin (Scheme 1.02).



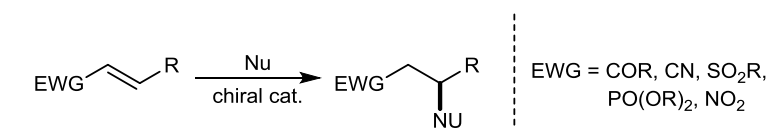
Scheme 1.02: 1,4-Addition to Alkenylpyridine

Thus, investigations into the potential of C=N containing azaarenes as activating groups for new catalytic enantioselective processes began to feature prominently in the Lam research group.¹⁰

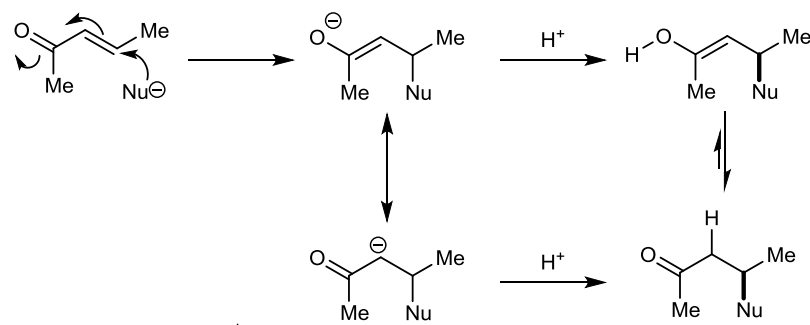
Prior to detailing our efforts on C=N containing azaarenes as activating groups in enantioselective catalysis, the literature precedence for nucleophilic additions to alkenylazaarenes is warranted.

1.2 Nucleophilic Conjugate Addition

One of the most powerful synthetic methods in modern day organic chemistry is the 1,4-addition of nucleophiles to electron deficient olefins. The mechanism of a typical 1,4-addition involves the attack of a nucleophile to a C=C double bond conjugated to an electron-withdrawing group, such as a carbonyl, followed by protonation (Scheme 1.03).



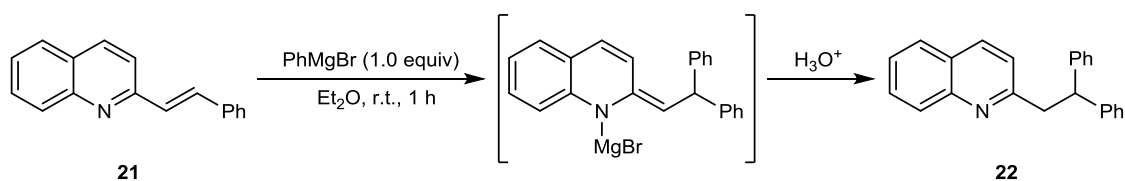
Mechanism:



Scheme 1.03: 1,4-Nucleophilic Conjugate Addition

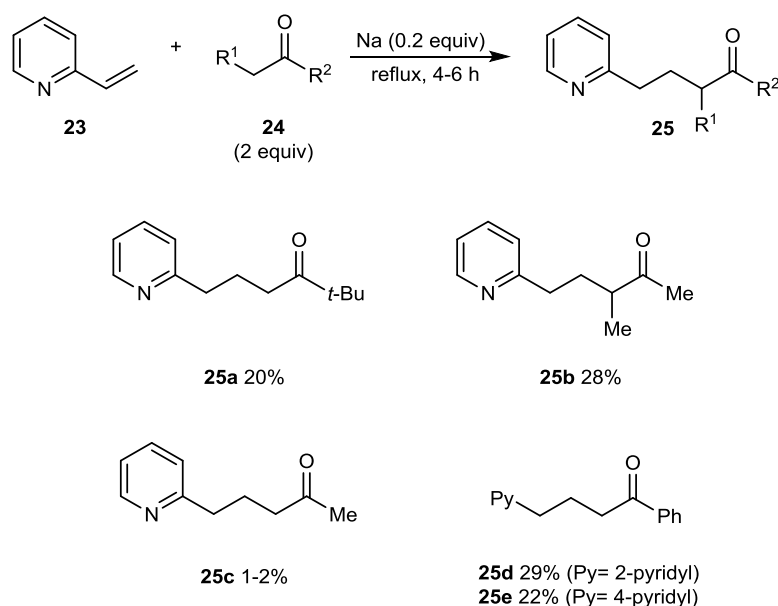
This methodology is commonly associated with alkenes activated by electron-withdrawing groups such as carbonyl, nitrile, nitro, sulfonyl or phosphonyl groups. Although less common, imines have also been successfully applied for this purpose.¹¹

The electron-withdrawing nature of the C=N moiety within an azaarene has long been recognised, dating back to 1933 when Hoffman demonstrated the addition of Grignard reagents to 2-alkenylquinolines (Scheme 1.04).¹²



Scheme 1.04: 1,4-Addition of Grignard Reagents to Alkenylquinoline¹²

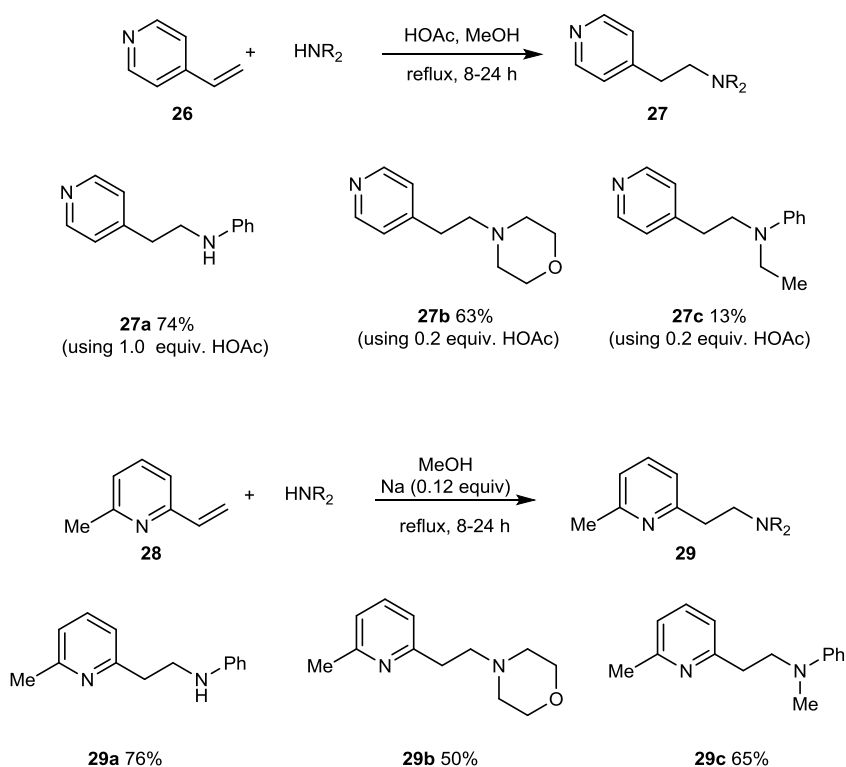
Levine and Wilt published one of the earliest successful nucleophilic additions of a carbonyl compound to alkenylazaarenes in 1953.¹³ They reported an alkylation of vinylpyridine (**23**) using a ketone enolate in the presence of sub-stoichiometric quantities of sodium metal (Scheme 1.05).



Scheme 1.05: Addition of Enolate to Vinylpyridine^{13a}

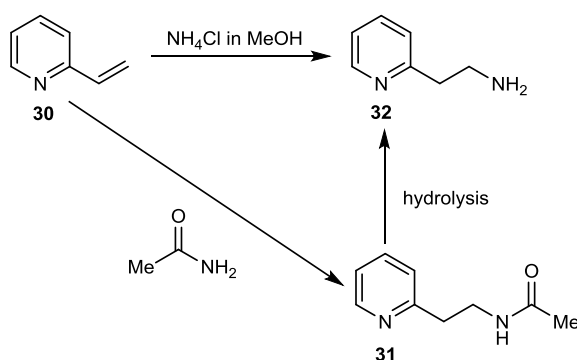
Mono-alkylated products **25a-25e** were obtained in low yields. They observed that when the starting material contained several α -hydrogens, multiple alkylations on vinylpyridine would occur. Experiments revealed that the extent of alkylation depended on the limiting reagent, as the product can be enolised and react with another molecule of vinylpyridine to furnish multi-alkylated azaarene products as side products. This side reaction can be suppressed by using excess ketone. Employing acetone in the reaction, they found almost negligible alkylation on the vinylpyridine (product **25c**). Alkylation of 4-vinylpyridine with acetophenone gave phenyl γ -(4-pyridyl)-propyl ketone (**25e**), demonstrating that the reaction does not depend on a nitrogen atom at the 2-position. There is only a small difference in yields obtained with the two different orientations of the pyridine substituent.

In 1956, Magnus and Levine published an extension of previous methodology from their laboratory to include the additions of amides, amines and nitriles to 4-vinylpyridines (**26**) and 2-methyl-5-vinylpyridine (**28**) (Scheme 1.06).¹⁴



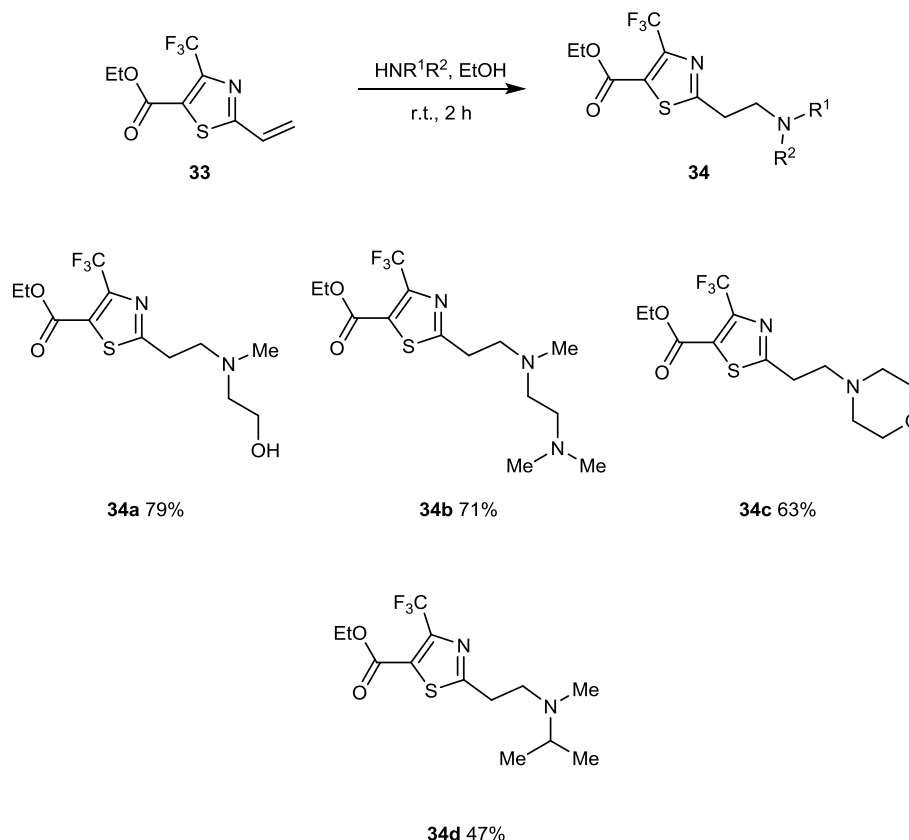
Scheme 1.06: Addition of Amines to Vinylpyridines¹⁴

For 4-vinylpyridine, glacial acetic acid catalysed the amine addition reaction, however, for amine additions to 2-methyl-5-vinylpyridine the use of sodium methoxide gave superior results (products **29a-29c**). The same paper also reported the formation of 2-(aminoethyl)pyridine (**32**) using two separate routes; the first involving the direct pyridethylation of ammonia with 2-vinylpyridine (**30**), and the second involving the synthesis of *N*-pyridylethylated amide (**31**) followed by hydrolysis to give 2-(aminoethyl)pyridine (**32**) (Scheme 1.07).



Scheme 1.07: Alkylation of 2-Vinylpyridine using Ammonia/ Acetamide¹⁴

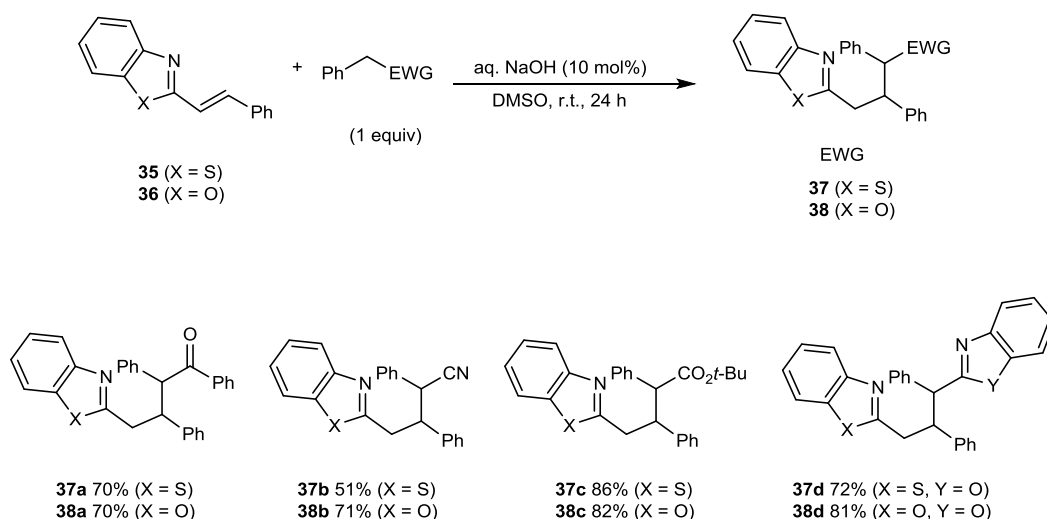
Investigations by Boy and Guernon into thiazole 5-carboxylic acid derivatives demonstrated that vinylthiazoles could undergo Michael-like additions (Scheme 1.08).¹⁵ In the absence of a catalyst, ethyl-4-(trifluoromethyl)-2-vinylthiazole-5-carboxylate precursor **33** underwent Michael-like additions with various secondary amines to give 2-aminoethyl-5-carbethoxythiazoles (**34a-34d**).



Scheme 1.08: Syntheses of 2-Aminoethyl-5-Carbethoxythiazoles¹⁵

Acyclic amines and diamines were the most effective addition partners giving products in good yields (products **34a-34b**) followed by cyclic amines with slightly diminished yields (product **34c**). Sterically hindered amines were also tolerated giving products in modest yields (product **34d**).

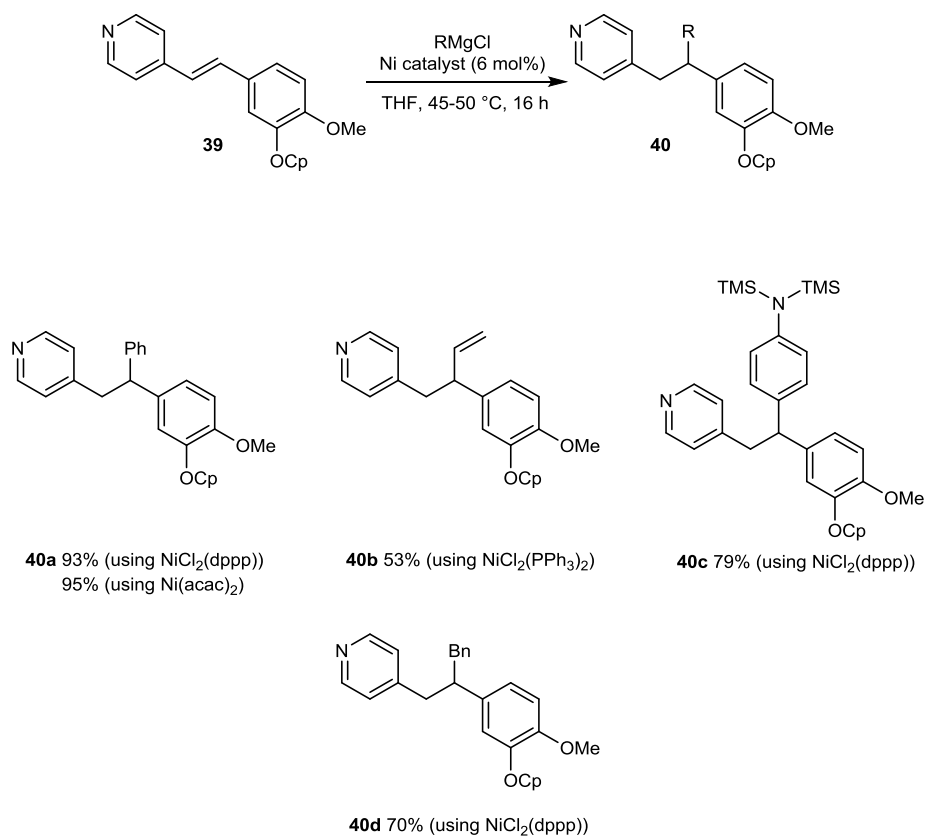
In 1983, Dryanska and Ivanov reported the conjugate addition of various nucleophiles to 2-styrylbenzothiazole (**35**) and 2-styryloxazole (**36**) in the presence of aqueous NaOH and DMSO (Scheme 1.09).¹⁶



Scheme 1.09: 2-Styrylbenzothiazoles and 2-Styrylbenzoxazoles as Michael-Acceptors¹⁶

Pronucleophiles including ketones, nitriles, esters and 2-benzylthiazole and 2-benzylthiazole were applied in these conjugate additions. Substitution at the β -position of the electrophile with a bulky phenyl group was also tolerated. The report showed that alkenyl benzoxazoles and benzothiazoles could effectively participate in 1,4-nucleophilic conjugate additions.

In 1998, Houpiš and co-workers presented the first catalytic addition of organometallic reagents to unactivated olefins **39** using nickel-catalysis to give arylation products in excellent yields (Scheme 1.10).¹⁷



Scheme 1.10: Nickel-Catalysed 1,4-Addition to 4-Alkenylpyridines using Grignard Reagent¹⁷

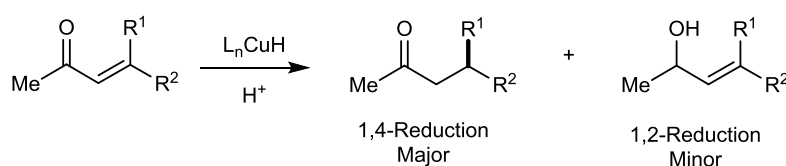
Efforts towards an asymmetric variant of this reaction were met with limited success (0-15% *ee*), despite screening a broad range of chiral ligands (bisphosphines, diamines, aminoalcohols, bisulphonamides and diols). However, this work suggests that highly enantioselective, nucleophilic 1,4-addition to alkenylpyridines may be possible.

A recent review by Klump¹⁸ summarizes extensive examples of the addition of nitrogen, oxygen, sulphur and carbon nucleophiles to a range of vinylazaarenes which all gives rise to achiral or racemic products. For those examples, enantioselective variants could not be developed due to the lack of β -substitution in the azaarene moiety. In comparison to vinylazaarenes, 1,4-addition to β -substituted alkenylazaarenes are much rarer, presumably for steric reasons.

1.2.1 Conjugate Reductions

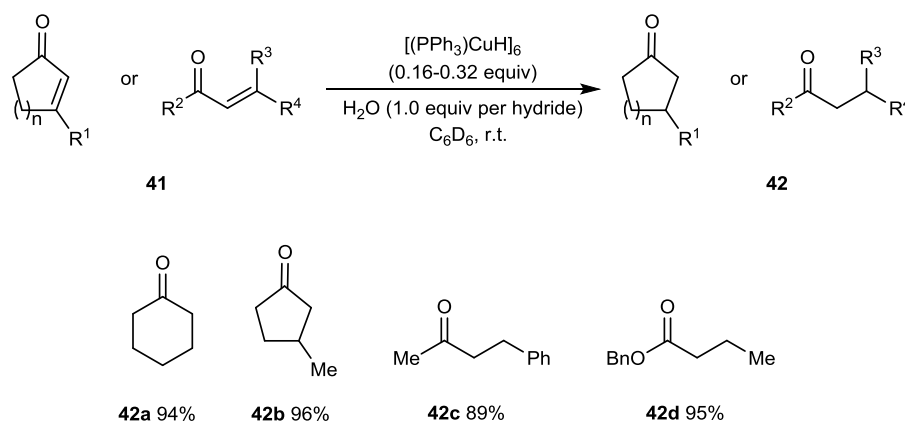
Under the umbrella of conjugate additions is a specific class of reactions called conjugate reductions. Catalytic reactions that reduce carbon-carbon double bonds to generate products with stereocenters *beta* to a carbonyl group with high enantioselectivities are of high value. Asymmetric conjugate reductions of α,β -unsaturated carbonyl compounds by organosilanes, mediated by complexes of rhodium, platinum, palladium and molybdenum have the ability to facilitate such reactions.¹⁹ However, the use of copper, a cheaper and more earth abundant metal, for the analogous transformation is a comparatively recent development.²⁰

Carbonyls, nitriles, sulfones, phosphonates, and nitro groups have all been shown to provide sufficient activation of the adjacent olefin towards conjugate reduction.²¹ Taking advantage of the carbophilic nature of copper, and through proper choice of reaction conditions, 1,4-reduction can be preferentially induced over 1,2-reduction (Scheme 1.11).²²



Scheme 1.11: Catalytic 1,4-Reduction of Alkenes

Copper(I) hydride is amongst the oldest metal hydride to be properly documented, dating back to 1844, first characterized by Wurtz as a red brown solid.²³ The most extensively studied copper hydride (CuH) is the hexameric phosphine stabilised complex, $[(\text{Ph}_3\text{P})\text{CuH}]_6$, first described by Osborn *et al.*²⁴ However, it was not until the late 1980s that use of CuH reagents gained notoriety as a highly reliable method of effecting conjugate reductions of unsaturated carbonyl derivatives though a seminal publication by Stryker *et al.*²⁵ In 1988, Stryker and co-workers reported the remarkable ability of the Osborn complex $[(\text{Ph}_3\text{P})\text{CuH}]_6$, to effect 1,4-conjugate reductions of various α,β -unsaturated carbonyl compounds **41** (Scheme 1.12).²⁵

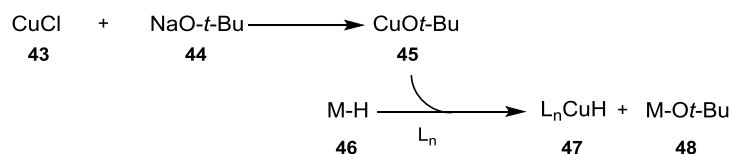


Scheme 1.12: Catalytic 1,4-Reduction Using Stryker's Reagent²⁵

The properties of this hexameric CuH complex include very mild reaction conditions, excellent functional group compatibility and overall efficiencies. All of this contributed to propelling $[(\text{Ph}_3\text{P})\text{CuH}]_6$, a beautiful crystalline red solid, to the status of “Reagent of the Year” in 1991. It is now commonly referred to as Stryker's reagent. It can be prepared in multi-gram quantities from four readily available and inexpensive precursor compounds (CuCl , NaOt-Bu , PPh_3 and H_2)²⁶ forming “environmentally friendly” sodium chloride and *tert*-butanol as by-products.²⁷

Exchanging PPh_3 for chiral non-racemic ligands generates chiral CuH species capable of catalysing conjugate reductions in an asymmetric manner. The synthesis of ligated CuH species relies on treatment of CuCl (**43**) with NaOt-Bu (**44**) to give CuOt-Bu (**45**). Addition of hydride source **46** (such as hydrosilane) to pre-formed **45** in the presence of a ligand leads to the generation of ligated CuH species **47** (Scheme 1.13). CuOt-Bu **45** is highly susceptible to oxidation therefore oxygen-free conditions are required when preparing CuH species **47**. Air-stable and commercially available $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ was found to be a suitable substitute for CuOt-Bu (**45**). $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (where Cu has an oxidation state of +2) is efficiently reduced to the CuH species **47** (where Cu has an oxidation state of +1) in the presence of a hydrosilane reductant and a ligand. Hydrosilanes are generally inexpensive and environmentally friendly and they have become a frequent source of stoichiometric hydride in modern CuH-catalysed reactions. Polymethylhydrosiloxane (PMHS),

1,1,3,3-tetramethyldisiloxane (TMDS), Fleming's silane (PhMe_2SiH), and phenylsilane (PhSiH_3) are examples of such reagents.



Scheme 1.13: Preparation of Ligated Copper Hydrides

Chiral bisphosphines have rapidly become the optimal ligands to form ligated CuH complexes. To date, virtually all success has come from a relatively small subset of either biaryl or ferrocenyl bisphosphine ligands. Advantageously, these ligands are available commercially both in quantity and in enantiomerically pure form; examples are illustrated in Figure 1.05.

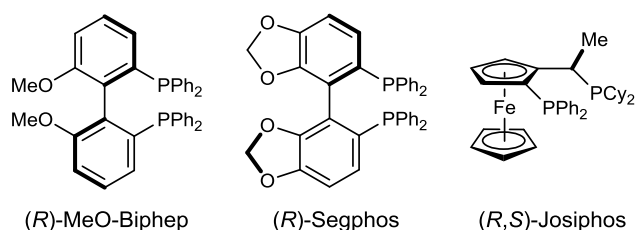
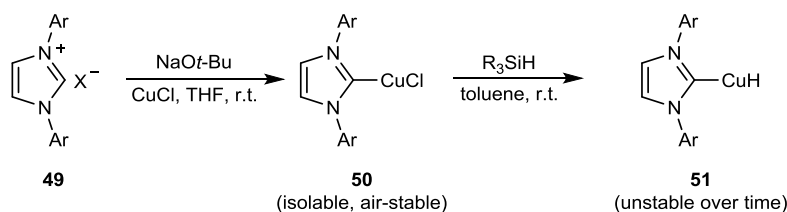
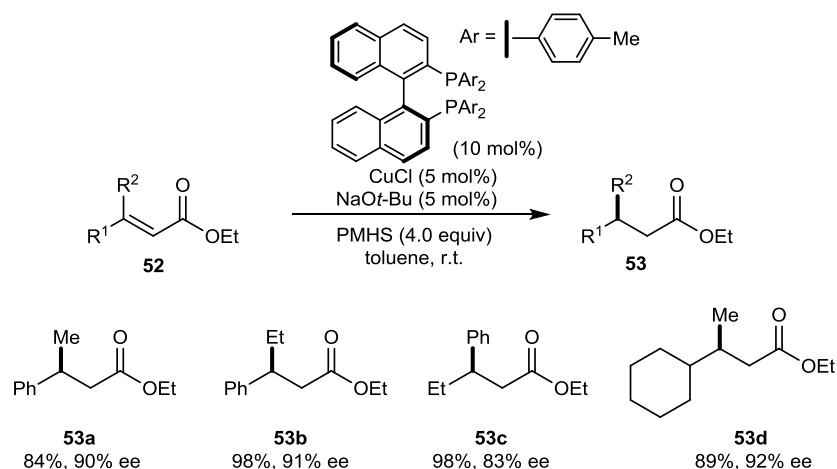


Figure 1.05: Bisphosphines used for enantioselective CuH Reactions

N-Heterocyclic carbenes (NHCs) have increased in popularity as an alternative to using bisphosphine ligands.^{20a} They are usually generated from the starting imidazolium salt **49** by treatment with base and CuCl, to give copper-carbene complex **50** followed by *in situ* conversion to the NHC-stabilized copper hydride **51** in the presence of a silane (Scheme 1.14). The use of air-stable and isolatable copper-carbene complex **50** in particular has made this an attractive alternative.²⁸ However, the use of chiral non-racemic carbene-based copper hydrides has not been applied in organic synthesis to date.^{20a}



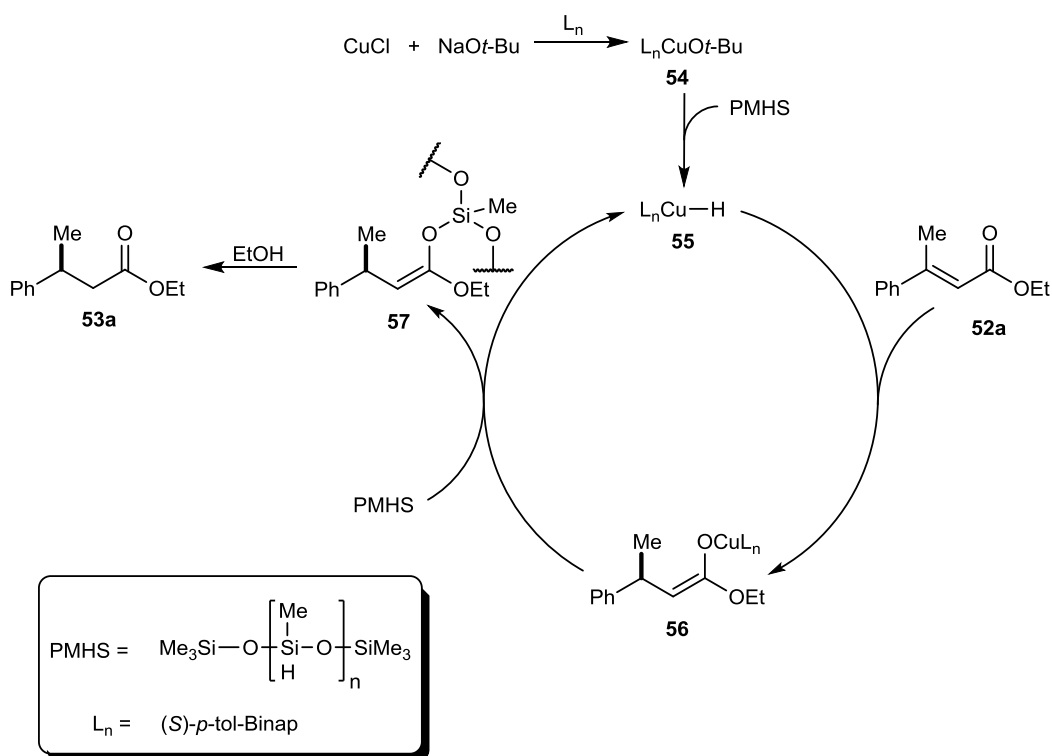
Enantioselective conjugate reductions catalysed by chiral bisphosphine-ligated CuH complexes and their application towards the synthesis of natural products and pharmaceutical drugs are well documented.^{20, 29} Detailed discussion on each report will not be covered in this thesis, rather only important breakthroughs and reports relevant to our study will be presented below.



Using CuCl as the copper source, NaOt-Bu as the base, and (*S*)-*p*-tol-BINAP as the chiral ligand; α,β -unsaturated esters **52** underwent smooth 1,4-conjugate reduction furnishing the corresponding saturated products (**53a-53d**) with high chemo- and enantioselectivity. *E*-(**52b**) and *Z*-(**52c**) isomers of substrates were examined and

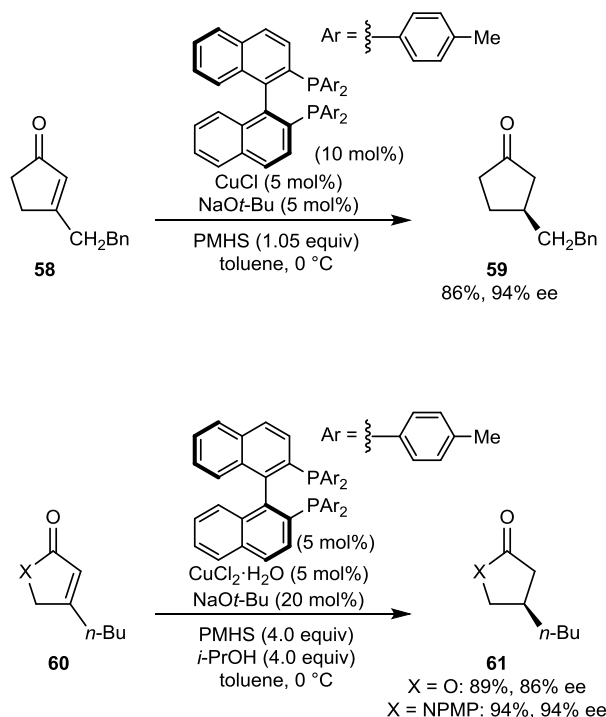
reacted to give predominantly opposite enantiomers **53b** and **53c** respectively both with high levels of enantioselection.

The catalytic cycle proposed by Buchwald for the conjugate reduction of enoate **52a** is illustrated in Scheme 1.16.^{30d} Treatment of CuCl with NaOt-Bu in the presence of a *p*-tol-BINAP forms (*p*-tol-BINAP)CuOt-Bu **54**. Addition of PMHS results in σ -bond metathesis between (*p*-tol-BINAP)CuOt-Bu **54** and PMHS to generate (*p*-tol-BINAP)CuH species **55**. Asymmetric conjugate reduction of enoate **52a** then occurs, resulting in formation of a copper enolate intermediate **56**, subsequent σ -bond metathesis with PMHS forms silylketene acetal **57** thus regenerating copper hydride **55**. The isolable product **57**, when quenched with a proton source such as EtOH, affords the enantioenriched ester **53a**.



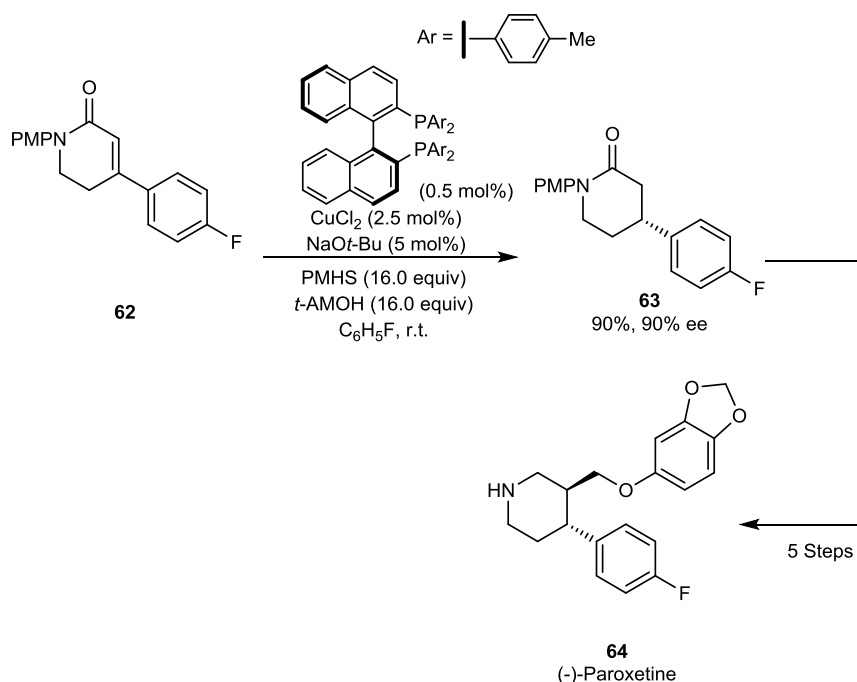
Scheme 1.16: Proposed Catalytic Cycle for CuH-Catalysed Conjugate Reductions^{30d}

The Buchwald group subsequently extended this methodology, applying it to enones **58**,^{30c} lactones and lactams **59** (Scheme 1.17).^{30b}



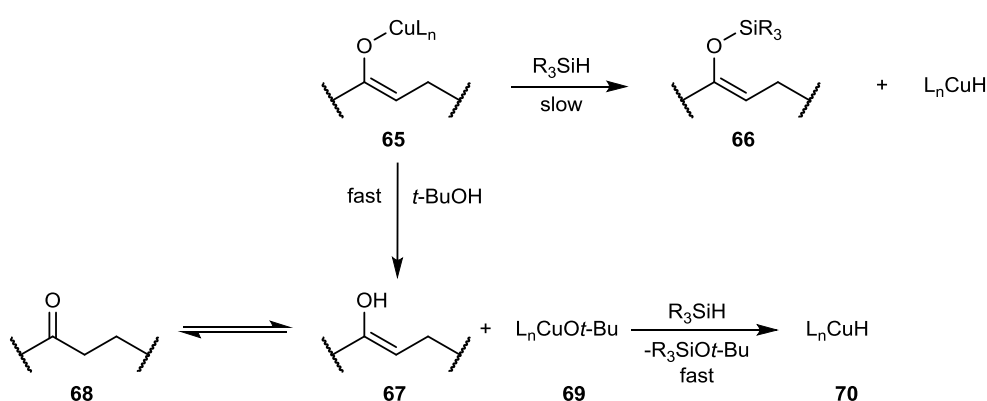
Scheme 1.17: Catalytic Enantioselective 1,4-Reduction of Enones, Lactones and Lactams^{30b, 30c}

High yields and excellent *ee*'s were again observed in the corresponding saturated products **59** and **60**. In the cases of lactones and lactams, they found air-stable $\text{CuCl}_2\cdot\text{H}_2\text{O}$ to be a suitable replacement for CuCl . Included in this publication was the utilisation of their methodology in the synthesis of the antidepressant drug (-)-Paroxetine (**64**).^{30b} The key reduction step of compound **62** in the synthetic route to the drug is presented in Scheme 1.18.



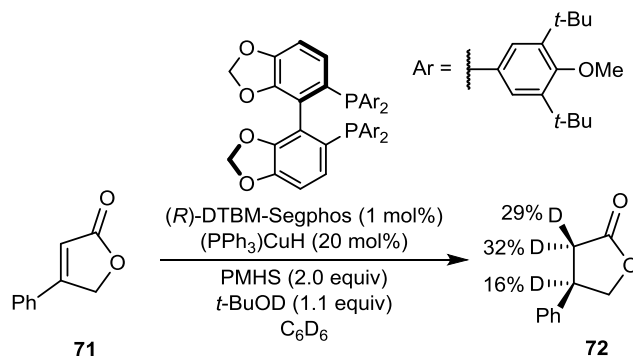
Scheme 1.18: Synthesis of (-)-Paroxetine by CuH-catalysed 1,4-Reduction^{30b}

Buchwald and co-workers also observed that the rate of conjugate reduction dramatically increased upon addition of alcohol additives.^{30b} In fact, several methods actually rely on the presence of bulky alcohol (e.g., *t*-BuOH) to enhance reaction rates.^{20a} The role of this additive is rapid protonation of the intermediate copper enolate **65** to give a copper alkoxide **69**, which readily undergoes σ -metathesis in the presence of excess silane regenerating copper hydride **70**, bypassing the slow σ -metathesis step between Cu-O (**65**) and Si-H (**66**) bonds, thus vastly improving the rate of reduction (Scheme 1.19).



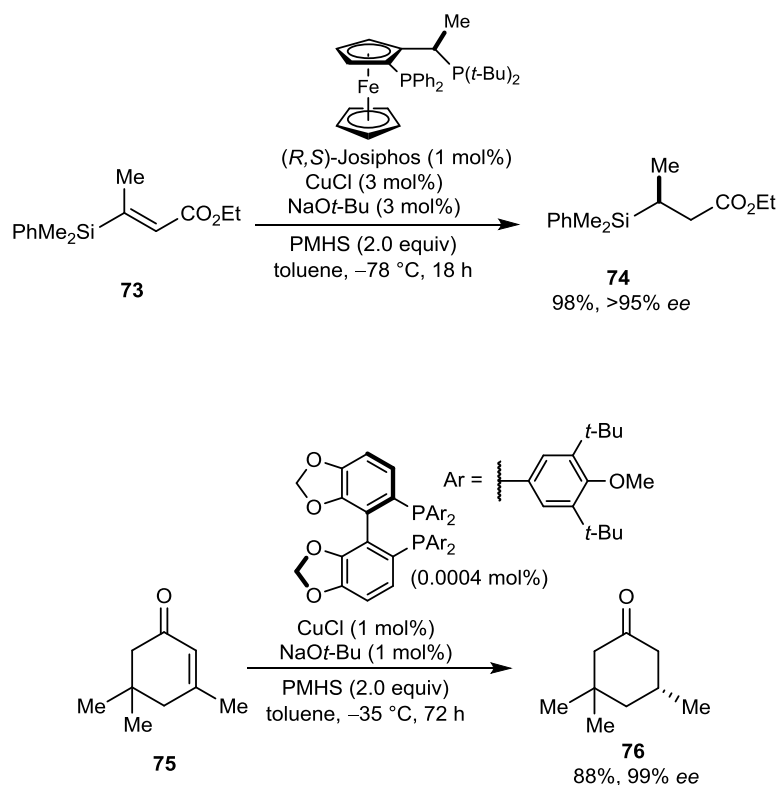
Scheme 1.19: Rationale for the Acceleratory Effect of Alcohol Additive^{30b}

This proposed mechanism was supported in deuterium studies using *t*-BuOD by the group of Lipshutz (Scheme 1.20).³¹ Asymmetric 1,4-hydrosilylation of unsaturated lactone **71** using *t*-BuOD revealed the majority of the deuterium was incorporated at the α -position, and only small quantities were incorporated at the β -position. As no exchange occurs between PMHS and *t*-BuOD, it appears that the rate enhancement results from the rapid protonation of the copper enolate by the alcohol rather than by the silane.



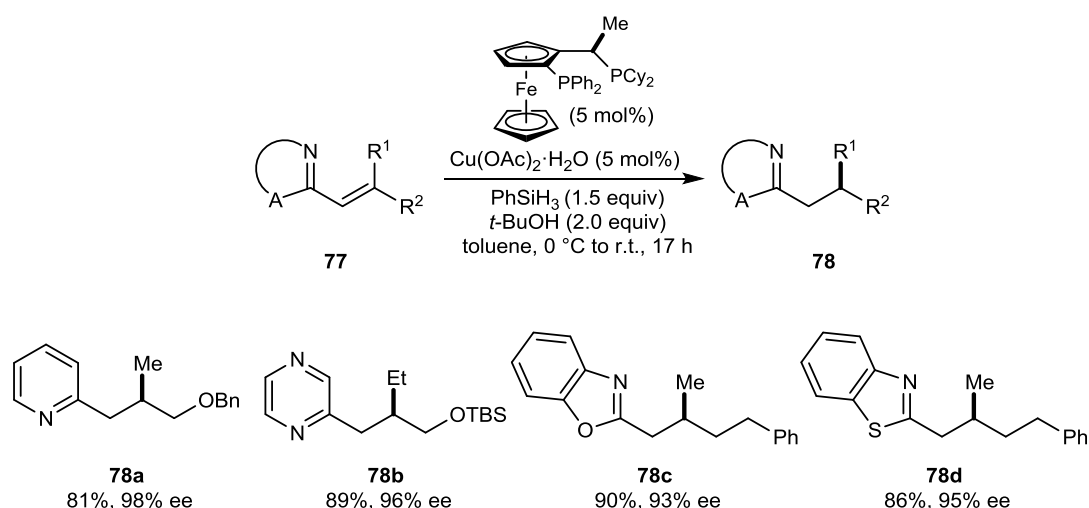
Scheme 1.20: Deuterium Experiment: Effect of Alcohol in CuH-Catalysed Reductions³¹

In a series of publications, Lipshutz and co-workers reported the CuH-catalysed conjugate reduction of acyclic and cyclic enones with high yields and enantioselectivities.³¹⁻³² Extensive ligand screening revealed that chiral biaryl bisphosphine ligands such as Segphos- and Josiphos-derived CuH species lead to higher levels of chiral induction than those obtained with the corresponding BINAP-CuH derivatives. Josiphos-type bisphosphines gave excellent results for acyclic enones **73**, whilst Segphos ligands were extremely efficient at reducing sterically hindered cyclic enones like isophorone (**75**) (Scheme 1.21).



Scheme 1.21: Catalytic Enantioselective 1,4-Reductions^{32c, 32d}

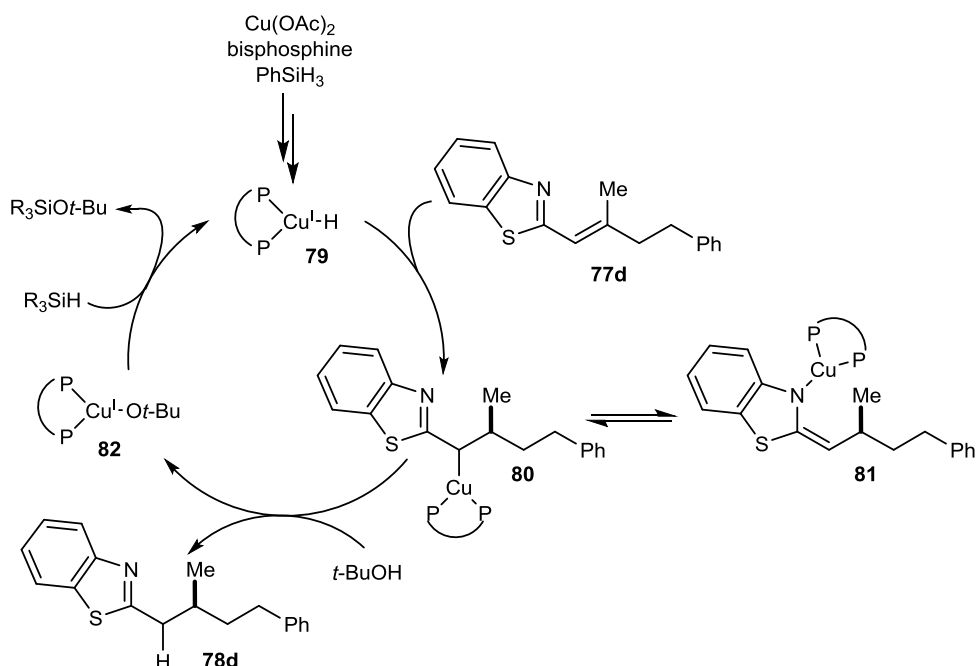
Examples of CuH-catalysed conjugate reductions involving the 1,4-reduction of polarized alkenes are present in literature and have been discussed so far. Lam and co-workers embarked on extending this methodology to include other important, yet underexploited electron-withdrawing groups on the acceptor, specifically, nitrogen-containing aromatic heterocycles. The importance of these structures has been previously discussed. Processes that exploit the ability of a suitably positioned C=N moiety within an azaarene to activate an adjacent alkene towards a catalytic enantioselective addition reaction were subsequently developed.^{10g, 10h} The first of these reports describes a highly enantioselective copper-catalysed reductions of β,β -disubstituted 2-alkenylazaarenes (Scheme 1.22).^{10h}



Scheme 1.22: Catalytic Enantioselective Reduction of β,β -Disubstituted Alkenylazaarenes^{10h}

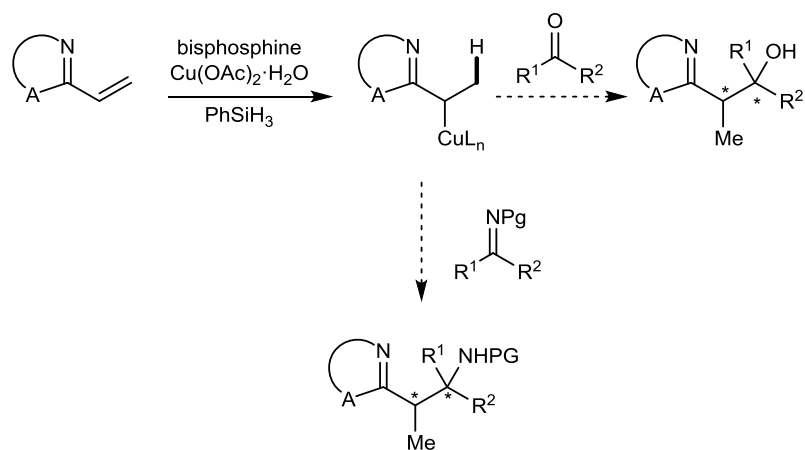
In the presence of catalytic $\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}$, a Josiphos bisphosphine ligand and stoichiometric quantities of *t*-BuOH, a series of β,β -disubstituted 2-alkenylazaarenes **77** were reduced using PhSiH_3 in high yields and with excellent enantioselectivities. A range of azaarenes were found to be compatible substrates including pyridine (**78a**), pyrazine (**78b**), benzoxazole (**78c**) and benzothiazole (**78d**). Additionally, the reaction tolerated functionalities including esters (**78a**) and silyl ethers (**78b**).

The catalytic cycle postulated for this reaction is relatively similar to the accepted mechanism for CuH-catalysed 1,4-reduction (Scheme 1.23). Since this reaction is likely to proceed via the intermediacy of organocopper species **80** that undergoes protonation with *t*-BuOH, it was questioned whether these intermediates could be trapped *in situ* with an alternative electrophile, extending this concept for tandem processes.



Scheme 1.23: Postulated Catalytic Cycle of CuH-Catalysed 1,4-Reduction of β,β -Disubstituted Alkenylazaarenes^{10h}

Conjugate reduction-alkylation, conjugate reduction cyclisation and conjugate reduction allylic substitution reactions were some of the avenues considered. Efforts ultimately focused on the conjugate reduction-aldol reaction and the Mannich reaction as the development of efficient catalytic asymmetric methods for the construction of chiral tertiary alcohols and chiral amines are highly desirable (Scheme 1.24).

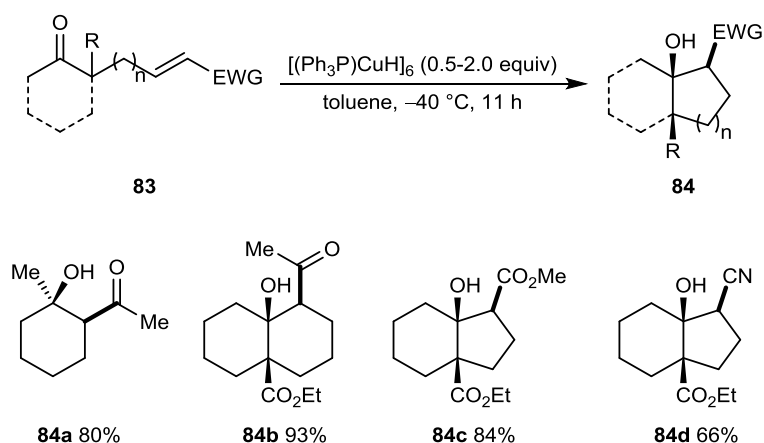


Scheme 1.24: Catalytic CuH-Catalysed Reductive Couplings^{10c, 33}

The aldol reaction is a classical method that has been routinely used for over 150 years. First reported by Borodin in 1869, it has become one of the most powerful and versatile methods in organic synthetic chemistry for the construction of carbon-carbon bonds. Conjugate reduction followed by an aldol reaction of the resulting enolate constitutes a reductive aldol reaction, which, when promoted by catalytic amounts of various transition-metal complexes and a hydride source, is a powerful tool for the creation of C-C bonds in a regio-, stereo- and enantioselective fashion. To date the catalysts for reductive aldol coupling based on rhodium,³⁴ cobalt,³⁵ iridium,³⁶ ruthenium,³⁷ palladium,³⁸ nickel,³⁹ indium,⁴⁰ and copper⁴¹ have been devised. Notably, rhodium and copper complexes play a dominant role in this field of organic chemistry.^{21a} The use of copper hydride also has inherent advantages of lower costs and higher selectivity. For the purpose of this report only copper-catalysed reductive aldol reactions will be discussed.

1.2.2 Intramolecular Copper-Catalysed Reductive Aldol Reactions

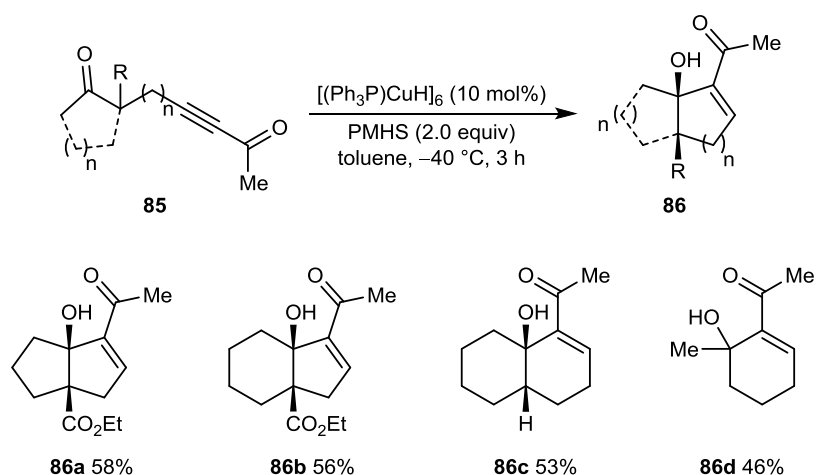
Chiu and co-workers applied the use of Stryker's reagent stoichiometrically and catalytically in CuH-catalysed reductive intramolecular aldol reactions.⁴² In 2001, they demonstrated that the copper enolates formed *in situ* by conjugate reduction of α,β -unsaturated carbonyl compounds with stoichiometric quantities of Stryker's reagent participate in an intramolecular aldol cyclisation furnishing five or six membered carbocyclic alcohols (Scheme 1.25).^{42b}



Scheme 1.25: Diastereoselective CuH-Mediated Reductive Aldol Cyclisation Using Stryker's Reagent^{42b}

The process is tolerant of a number of electron-withdrawing groups conjugated to the alkene including ketones, esters and nitriles (products **84a-84d**). The reaction proceeded to form new 5- or 6-membered carbocycles with high diastereoselectivity and with exclusively *cis*-stereochemistry. The report also noted *E*- and *Z*- isomeric substrates delivered products with the same stereochemistry; however the *trans*-isomer reacted at a faster rate than its *cis*-isomeric counterpart.

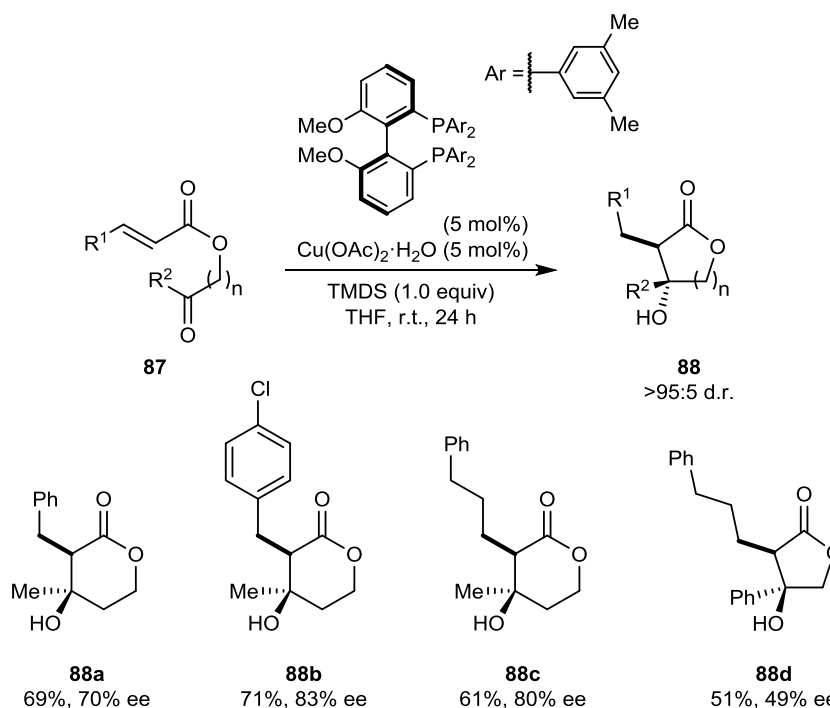
Subsequently in 2004, the same group reported a catalytic use of Stryker's reagent in a reductive aldol cyclisation of alkynediones **85** (Scheme 1.26).^{42a}



Scheme 1.26: Diastereoselective CuH-Catalysed Reductive Aldol Cyclisation using Stryker's Reagent^{42a}

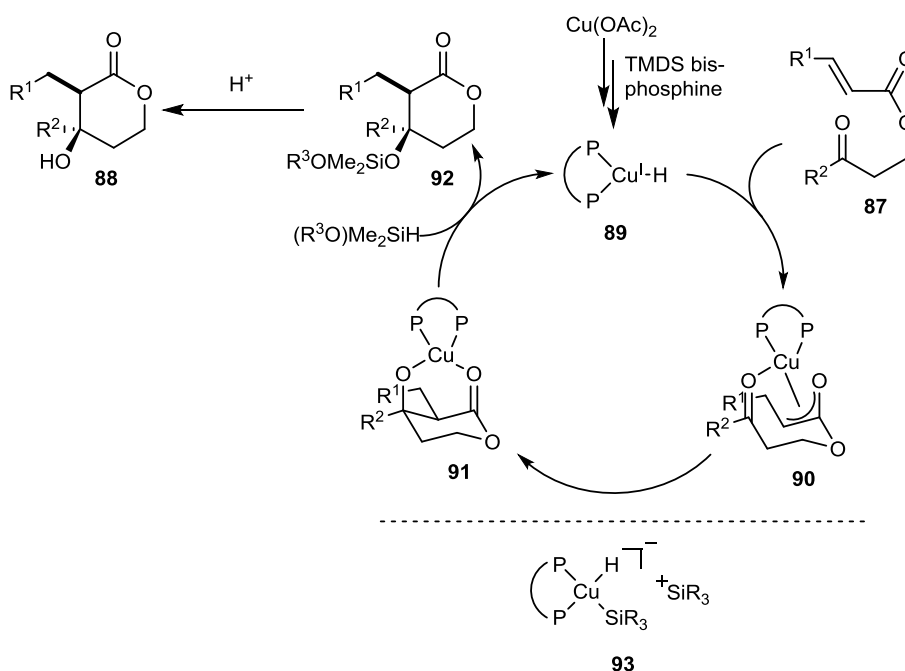
Using sub-stoichiometric quantities of Stryker's reagent and PMHS as the hydride source, the cyclisation of alkynediones proceeded efficiently to furnish β -hydroxycycloalkenone (products **86a-86d**) in modest yields. The products were formed with predominately *cis*-stereochemistry in all cases examined. The β -hydroxycycloalkenones products are complementary to those formed from the intramolecular Baylis-Hillman reaction. β -Substituted enones and ketones are poor Michael-acceptors and electrophiles respectively for the Baylis-Hillman reaction, conversely the reductive aldol cyclisations of related alkynones **86** mediated by Stryker's reagent occurred at low temperatures and mild conditions.

In 2005, Lam and co-workers described the first diastereo- and enantioselective CuH-catalysed reductive aldol cyclisation mediated by bisphosphine ligands.⁴³ The cycloreduction gave β -hydroxylactones **88a-88d** with excellent diastereoselectivity (>95:5 in all cases) and modest to good enantioselectivities (Scheme 1.27).



Scheme 1.27: Intramolecular Reductive Aldol Reaction of α,β -Unsaturated Esters with Ketones⁴³

During this investigation they detected small quantities of the uncyclised side product that had undergone reduction at the enoate and in some cases at the ketone resulting in moderate yields. This observation indicates that the rate of σ -bond metathesis of the intermediate copper enolate with the siloxane is competitive with the rate of aldol cyclisation. A plausible catalytic cycle for the process was included in the communication (Scheme 1.28).

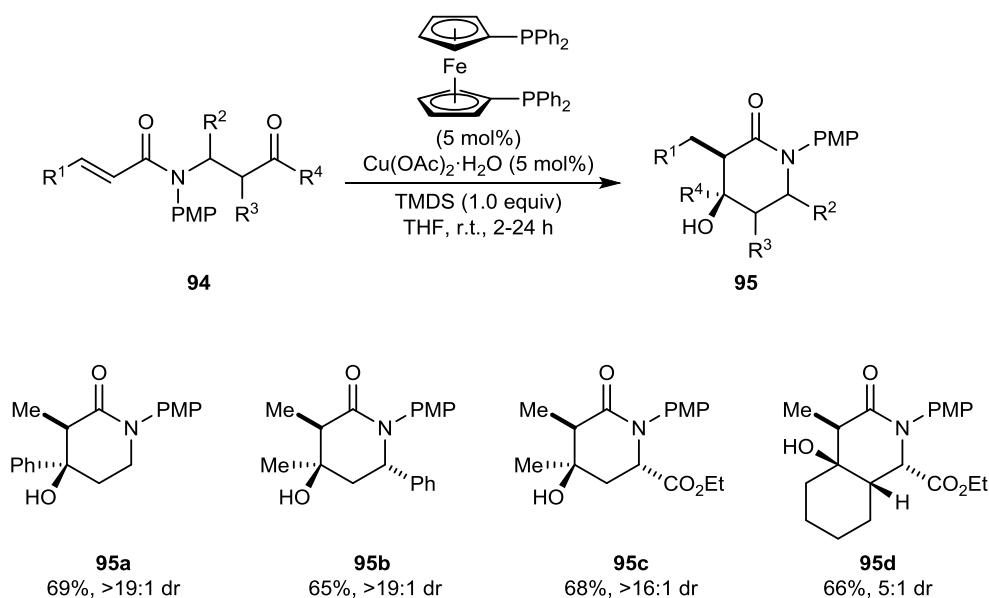


Scheme 1.28: Proposed Catalytic Cycle of CuH-Catalysed Aldol Cycloreduction⁴³

$\text{Cu}(\text{OAc})_2$ in the presence of bisphosphine and TMDS is reduced to generate a CuH-bisphosphine complex **89**, which then engages in hydrometalation with substrate **87** to generate the copper enolate **90**. Carbonyl addition results in the copper aldolate **91**, which then undergoes σ -bond metathesis with the siloxane to liberate the silylated product **92** (silyl deprotection occurs upon work-up to give the product **88**), regenerating the CuH-bisphosphine complex **89**. The observed stereochemistry is postulated to arise from preferential formation of the *Z*-copper enolate, coupled with chelation in the carbonyl addition step (as in **91**).

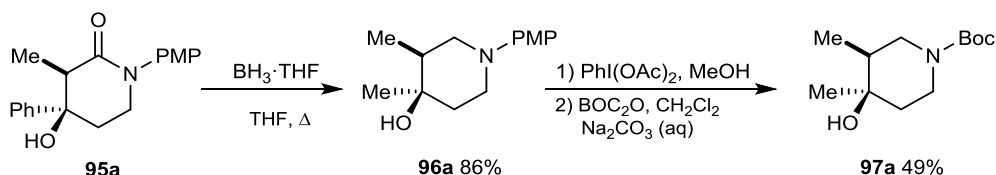
This methodology was extended for the synthesis of 4-hydroxypiperidin-2-ones, formed through cycloreduction of α,β -unsaturated keto-amides **94** (Scheme 1.29).⁴⁴

N-Alkyl-*N*-arylamides bearing no stereocenters such as substrate **94a** (where R² and R³ = H) cyclised efficiently to give products **95a** in a good yield and excellent diastereoselectivity. Enantioenriched acrylamide containing pre-existing stereocenters cyclised to give the corresponding piperidinones **95b-95d** respectively, in moderate to excellent levels of 1,2- and 1,3-asymmetric induction.



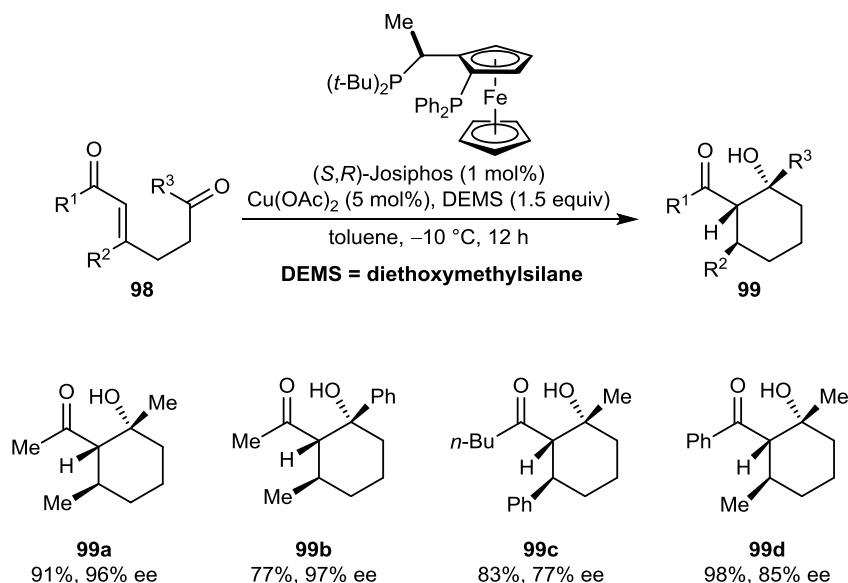
Scheme 1.29: Intramolecular Reductive Aldol Reaction of α,β -Unsaturated Amides⁴⁴

Further transformations of the β -hydroxy piperidinones were performed to demonstrate the synthetic utility of this methodology (Scheme 1.30). Reductive removal of the carbonyl group of **95a** by treatment with borane at reflux allows entry into the piperidine ring system **96a**, which is a structural feature of many natural products and biologically active compounds.⁴⁵ Oxidative removal of the PMP group on **96a** followed by *in situ* treatment of the resulting amine with Boc₂O furnished piperidine **97a** in modest yield.



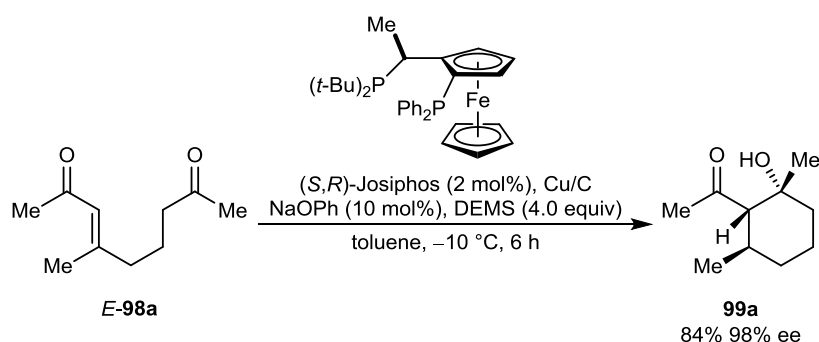
Scheme 1.30: Conversion of Piperidinone Products into Piperidines⁴⁴

In 2008, Lipshutz and co-workers reported the first CuH-catalysed intramolecular reductive aldol reactions of acyclic β,β -disubstituted keto enones **98**, generating chiral compounds containing three contiguous stereocenters **99a-99d** (Scheme 1.31).⁴⁶



Scheme 1.31: CuH-Catalysed Reductive Aldol Reactions of β,β -Disubstituted Keto Enones⁴⁶

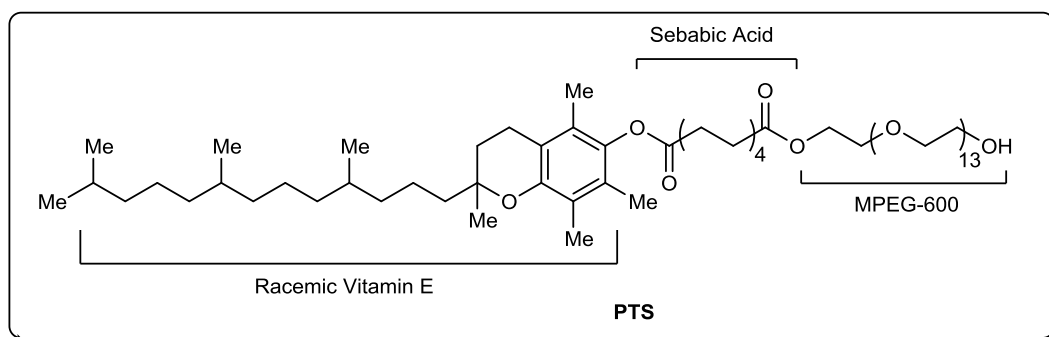
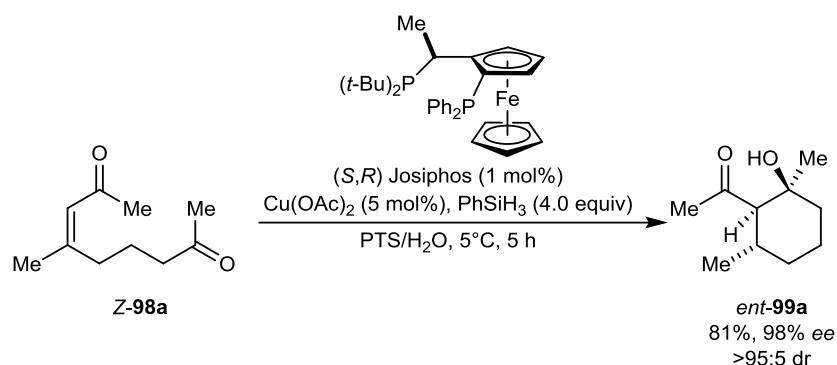
An alternative copper-catalysed cycloreduction method furnished cyclised product **99a**, employing heterogeneous Cu/C in the presence of NaOPh and stoichiometric hydride DEMS in toluene (Scheme 1.32).



Scheme 1.32: Heterogeneous Reductive Aldol Reactions⁴⁶

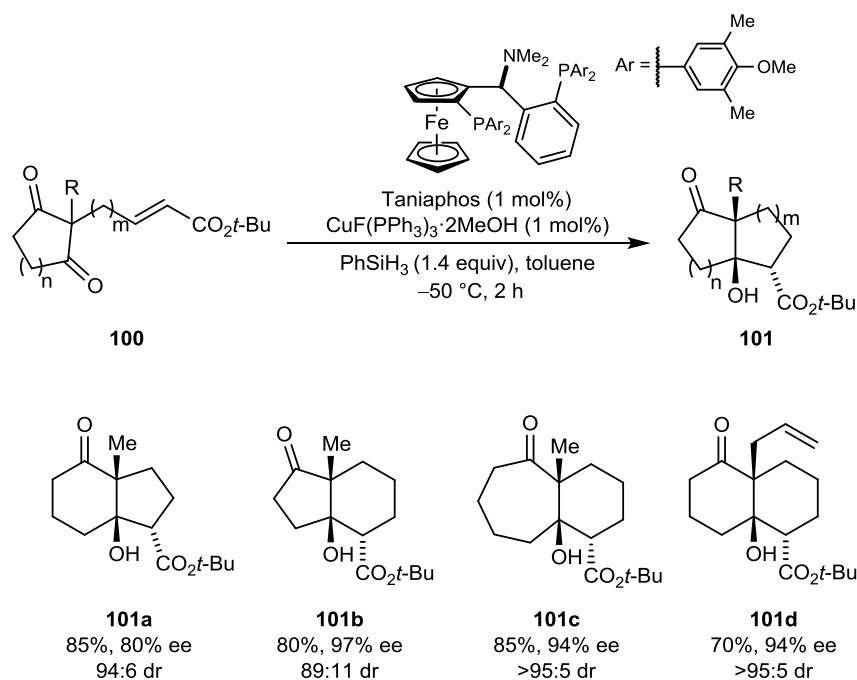
They also reported that the asymmetric reductive aldol reaction could be run entirely in water despite the water-insoluble nature of adduct **Z-99a** through the addition of a

surfactant; a nanomicelle-forming PTS (a non-ionic, vitamin E based surfactant; 2% by weight) (Scheme 1.33). In the presence of stoichiometric PhSiH_3 1,4-reduction/cyclisation led to adduct *ent*-**99a** with excellent yields and enantioselectivity.



Scheme 1.33: Aqueous Asymmetric Reductive Aldol Reactions⁴⁶

In 2009, Riant *et al.* described a CuH-catalysed reductive aldol cyclisation of diketoesters (Scheme 1.34).⁴⁷ The domino process catalysed by a CuH-Taniaphos complex, in the presence of PhSiH_3 furnished highly diastereoselective and enantioselective bicyclic products with excellent yields (**101a-101d**).



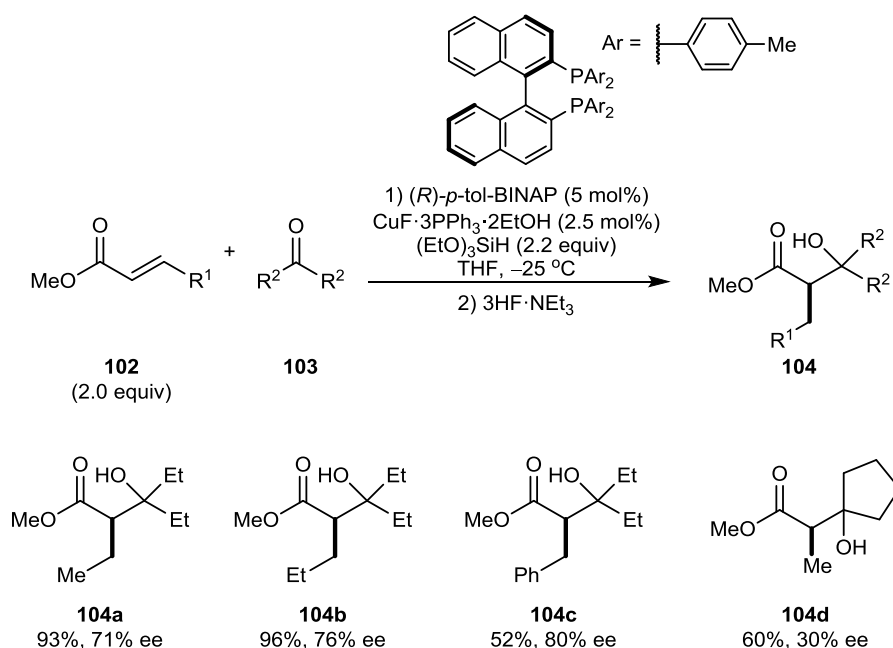
Scheme 1.34: Enantioselective CuH-Catalysed Reductive Aldol Cyclisation of Diketo-Esters⁴⁷

In literature there are abundant examples of CuH-catalysed intramolecular reductive aldol cyclisations, but there are comparatively fewer reports on intermolecular reductive aldol reactions. The formation of five or six- membered rings in intramolecular cyclisations serves as a strong kinetic driving force for the reaction to occur. However, in analogous intermolecular couplings, the reaction is entropically less favourable due to the absence of this driving force. Nevertheless, enantioselective CuH-catalysed reductive aldol couplings using organosilanes as the hydride source have been reported previously.

1.2.3 Intermolecular Copper-Catalysed Reductive Aldol Reactions

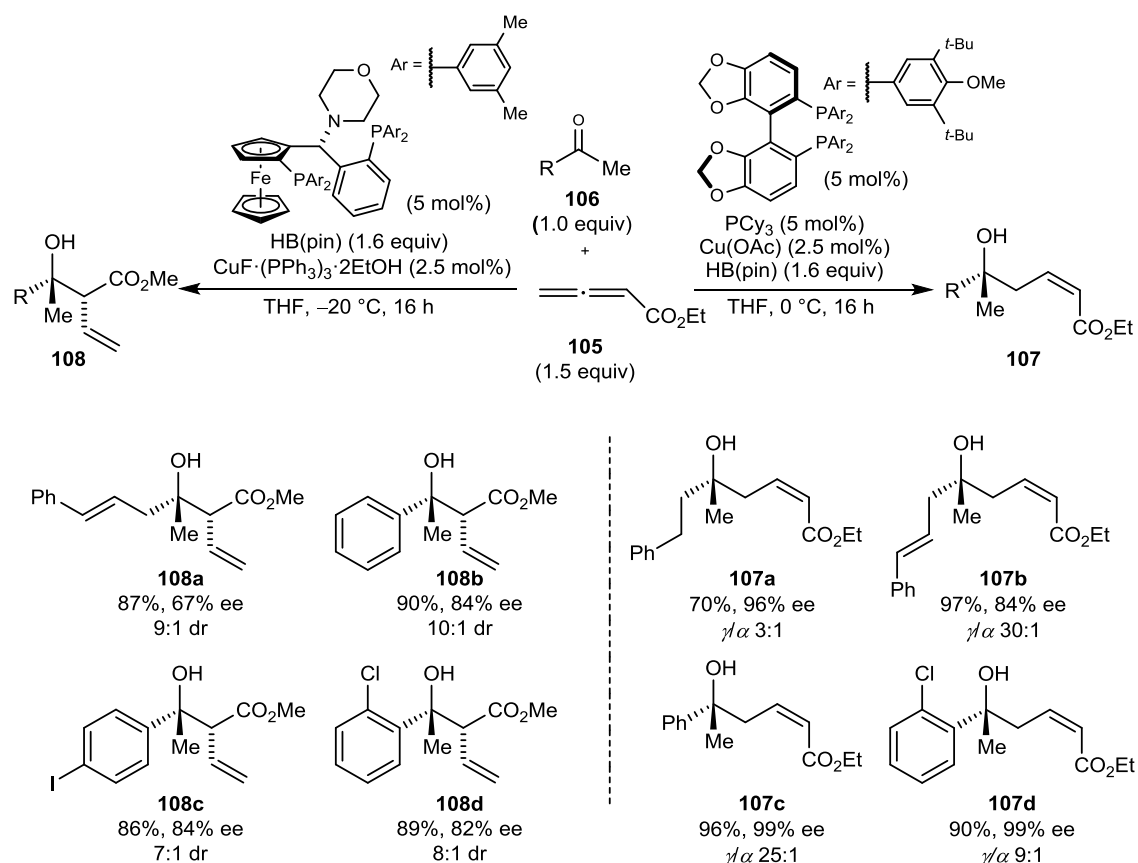
In 2006, Shibasaki and co-workers reported an enantioselective intermolecular reductive aldol reaction to ketones using a chiral CuH-bisphosphine complex (Scheme 1.35).⁴⁸ Initial experiments using methyl acrylate and acetophenone did not produce meaningful enantio- and diastereoselectivity; therefore efforts were focused on asymmetric induction at the α -position using symmetrical ketones **103**. Modest enantioselectivities and good to high yields were observed with acyclic ketones

(products **104a-104c**). The use of a cyclic ketone afforded the coupled product **104d** with significantly diminished enantioselectivity and lower yields. Nevertheless, the report successfully demonstrated the intermolecular CuH-catalysed reductive coupling of α,β -unsaturated esters with ketones.



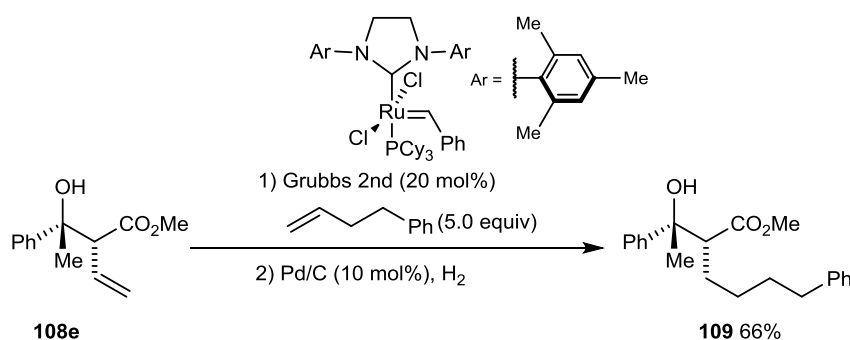
Scheme 1.35: Asymmetric Induction at α -Position in Reductive Aldol Reaction to Symmetric Ketones⁴⁸

A subsequent publication by the same group reported the reductive coupling of allenic esters **105** to ketones **106** to furnish enantiomerically enriched tertiary alcohols (Scheme 1.36).⁴⁹ This publication highlighted a dramatic ligand effect that allowed the selective synthesis of two constitutional isomers (α - and γ -aldol) depending on the ligand employed. In the presence of CuOAc, (*R*)-DTBM-Segphos, PCy₃ and pinacolborane in THF, allenic esters **105** reacted with various ketones to selectively produce γ -*cis*-tertiary alcohols **107a-107d**. Changing the reaction conditions to CuF(PPh₃)₃·2EtOH, Taniphos ligand and pinacolborane in THF led to the selective production of α -products **108a-108d** in excellent yields and modest to high enantioselectivity. They demonstrated that the product distribution (α - and γ -aldol) could be switched depending on the structure of the chiral bisphosphine ligand, though no explanation of the reaction mechanism and how the choice of ligand affects the product outcome was provided in the communication.



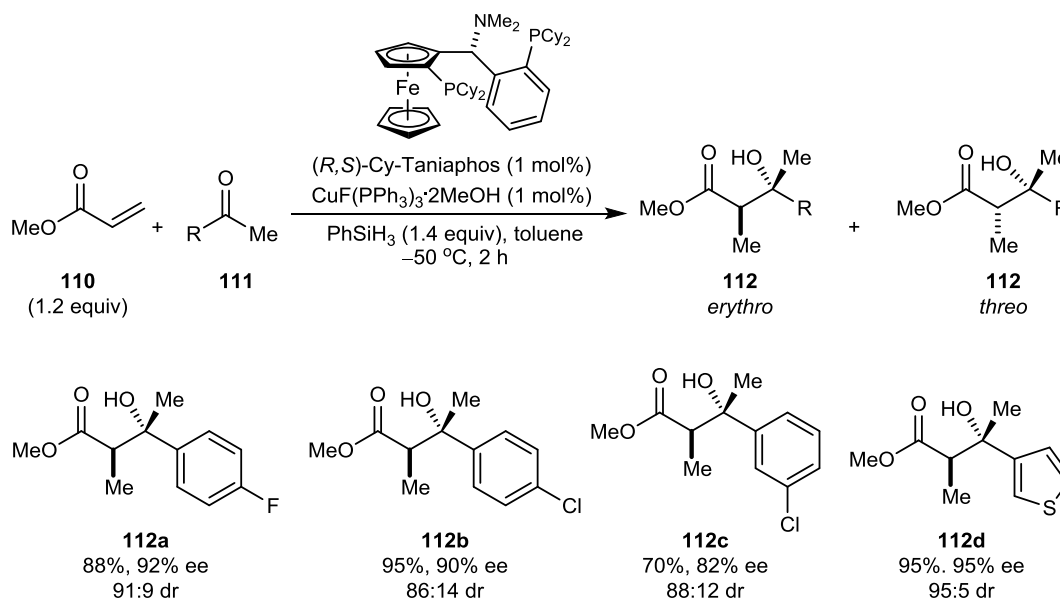
Scheme 1.36: CuH-Catalysed Reductive Aldol Reaction of Allenic Esters to Ketones⁴⁹

The terminal alkene in **108** provides a functional handle for further derivatisation. For example, alcohol **108e** was converted to **109** in a chain extension sequence involving cross-metathesis without any epimerisation at the α -position or racemisation (Scheme 1.37).



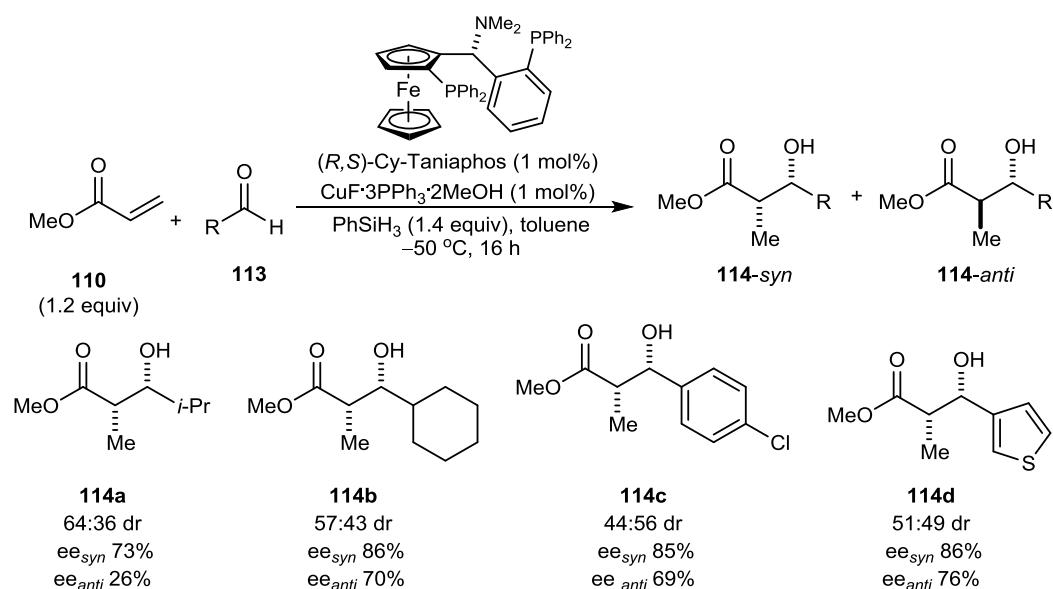
Scheme 1.37: Conversion of α -Vinyl Aldol Product⁴⁹

In 2006, Riant *et al.* also published a report on copper-catalysed asymmetric reductive aldol coupling of α,β -unsaturated esters with ketones. In the presence of $\text{CuF}(\text{PPh}_3)_3 \cdot 2\text{MeOH}$ as the precatalyst, (*R,S*)-Cy-Taniaphos as the chiral ligand and PhSiH_3 as the stoichiometric reductant, various aromatic ketones **111** participated in a reductive aldol reaction with methyl acrylate (**110**) affording products **112a-112d** with high diastereo- and enantiocontrol (Scheme 1.38).^{41b} The major isomer formed under these reaction conditions was the *erythro* isomer.



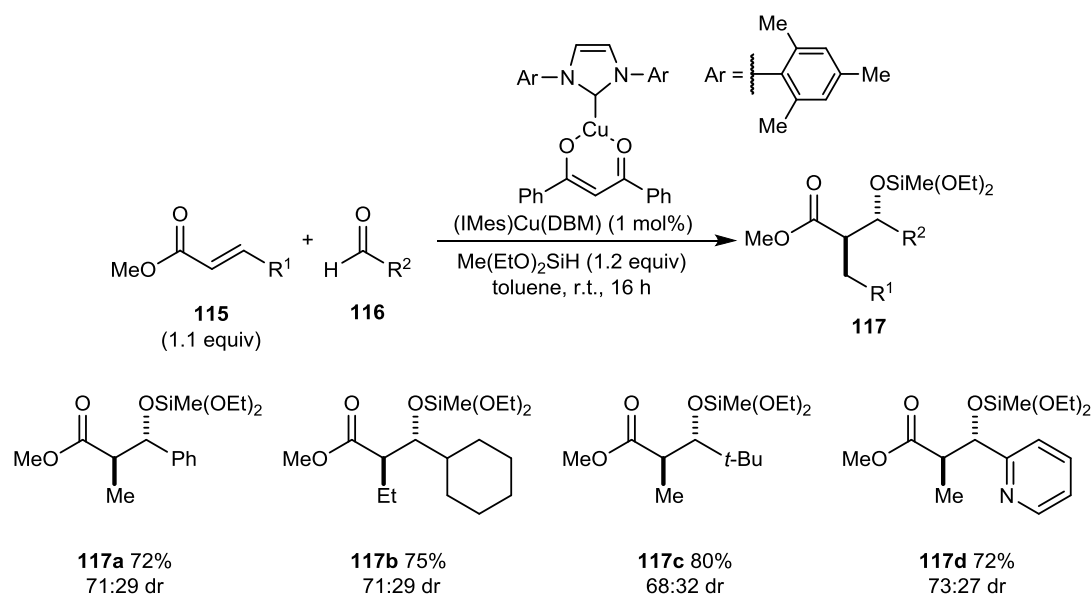
Scheme 1.38: Cu-Catalysed Asymmetric Reaction of Aryl Methyl Ketones and Methyl Acrylate⁵⁰

Riant *et al.* subsequently applied the catalytic system described above to the *syn*-selective reductive coupling of aldehydes **113** with methyl acrylate (**110**) (Scheme 1.39).⁴⁷ Substrate scope include acyclic aliphatic aldehydes (product **113a**), cyclic aliphatic aldehydes (product **113b**), aromatic aldehydes (product **113c**) and heteroaromatic aldehydes (product **113d**); all participated successfully in the reaction with conversion >99%. Isolated yields were reported to be in the range of 74-99% for products **113a-113d**. Diastereoselectivity for this reaction was poor, but good enantioselectivities were observed. The ability to selectively reduce α,β -unsaturated esters and then couple with an aldehyde is notable given the high reactivity of aldehydes towards 1,2-reduction.⁵¹



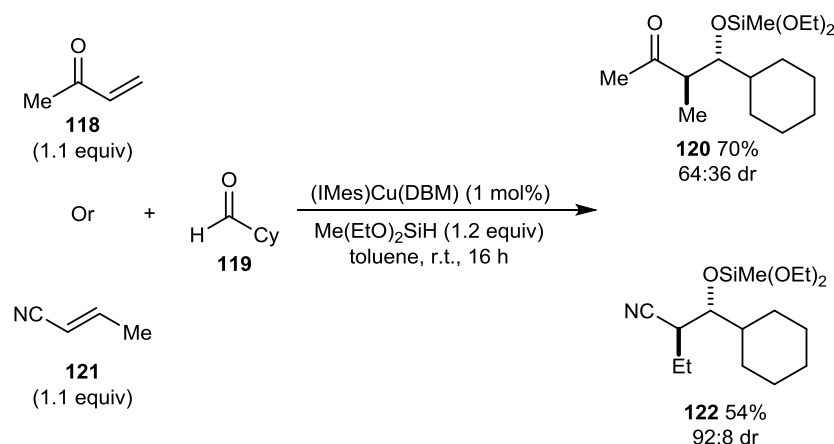
Scheme 1.39: CuH-Catalysed Reductive Coupling of Methyl Acrylate with Aldehydes⁴⁷

Having established an efficient catalytic system for the CuH-catalysed reductive aldol coupling of methyl acrylates with aldehydes and ketones using various chiral bisphosphine ligands, Riant *et al.* turned their attention to the performance of NHC ligands in such catalytic reactions. Using substoichiometric quantities of achiral NHC-ligated copper catalyst (IMes)Cu(DBM) the reductive coupling of α,β -unsaturated esters and aldehydes were realised (Scheme 1.40).⁵²



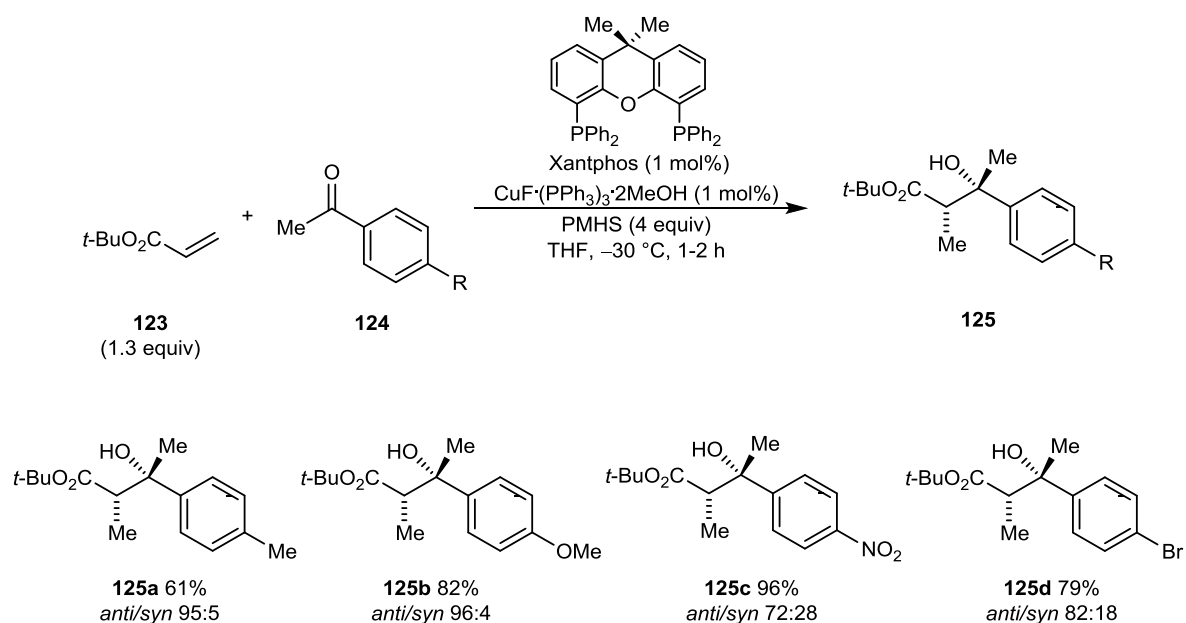
Scheme 1.40: NHC Cu-Catalysed Reductive Aldol Reaction⁵²

Good yields were observed with various aliphatic and (hetero)aromatic aldehydes, with the *anti*-isomer being the dominant product in all cases examined (products **117a-117d**). Diastereoselectivities were modest (up to 73:27 dr), but the reaction was highly chemoselective. They also examined other electron-withdrawing functional groups on the Michael acceptor (Scheme 1.41). Using unsaturated ketone **118** with cyclohexane carboxaldehyde (**119**) gave the corresponding product in good yield and promising diastereoselectivity (product **120**). Nitrile **121** coupled with cyclohexane carboxaldehyde (**119**) to give product **122** in modest yield and excellent diastereoselectivity.



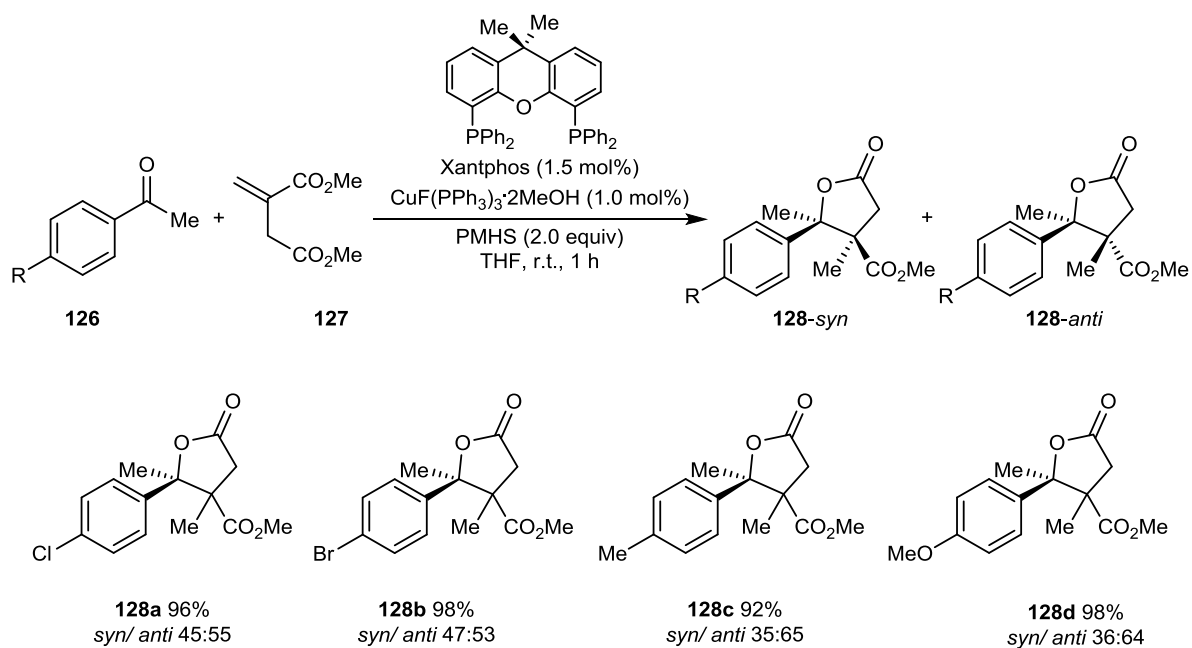
Scheme 1.41: NHC Cu-Catalysed Reductive Aldol Reaction with Various Electrophilic Alkenes⁵²

In 2013, Li and co-workers described a CuH-catalysed domino reaction of *tert*-butyl acrylate with ketones in the presence of hydrosilane PMHS and CuH-Xantphos complex (Scheme 1.42).⁵³ The reaction was tolerant of electron-donating groups furnishing products with good diastereoselectivities (product **125a-125b**). Substrates with electron-withdrawing groups on the ketone furnished products with excellent yields but with slightly diminished diastereoselectivities (products **125c-125d**).



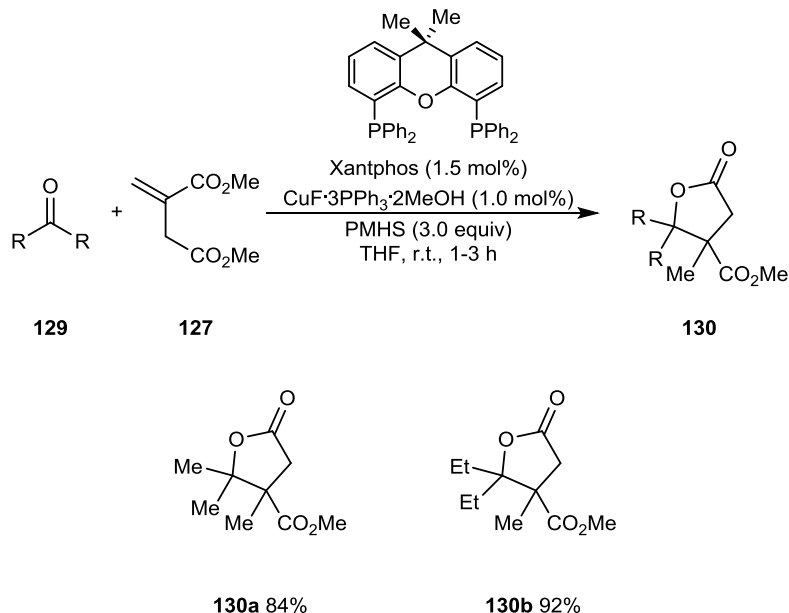
Scheme 1.42: NHC Cu-Catalysed Reductive Aldol Reaction with Various Electrophilic Alkenes⁵³

In a more recent publication, Li and co-workers described a CuH-catalysed reductive aldol addition of α,β -unsaturated diesters to furnish lactones.⁵⁴ Using substituted acetophenones **126** and dimethyl itaconate (**127**) in the presence of $\text{CuF}(\text{PPh}_3)_3 \cdot 2\text{MeOH}$ -Xantphos derived catalyst and stoichiometric PMHS furnished separable lactones (products **128a-128d**) in excellent yields (Scheme 1.43). The reaction was tolerant of electron-withdrawing groups and electron-donating groups on the aryl ring of the ketone.



Scheme 1.43: Conjugate Aldol Lactonization Domino Reaction of Dimethyl Itaconate⁵⁴

Although diastereoselectivities were poor, it is a useful methodology for preparing lactones with an *exo*-ester moiety. Symmetrical ketones gave products with a single stereocentre in high yields (Scheme 1.44).

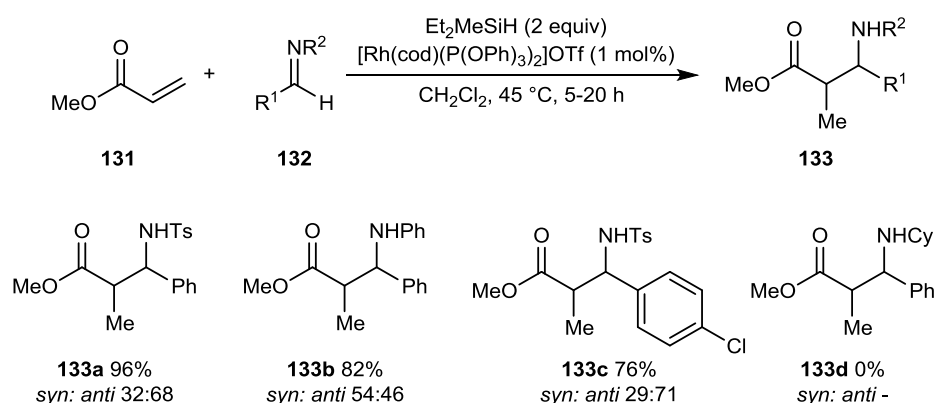


Scheme 1.44: Conjugate Aldol Lactonization Domino Reaction of Dimethyl Itaconate⁵⁴

1.3 Reductive Mannich Reactions

Compared with the Cu(I)-catalysed intermolecular reductive aldol reactions of α,β -unsaturated carbonyl compounds previously discussed, the corresponding reductive Mannich reactions are less well studied. Mannich-type reactions of an aldimine with an enolate component are some of the most important and versatile tools to construct β -amino carbonyl compounds.⁵⁵ The products of the Mannich reaction have been used for the enantioselective synthesis of several important nitrogen containing products such as amino acids, amino sugars, imino sugars and amino alcohols.⁵⁶

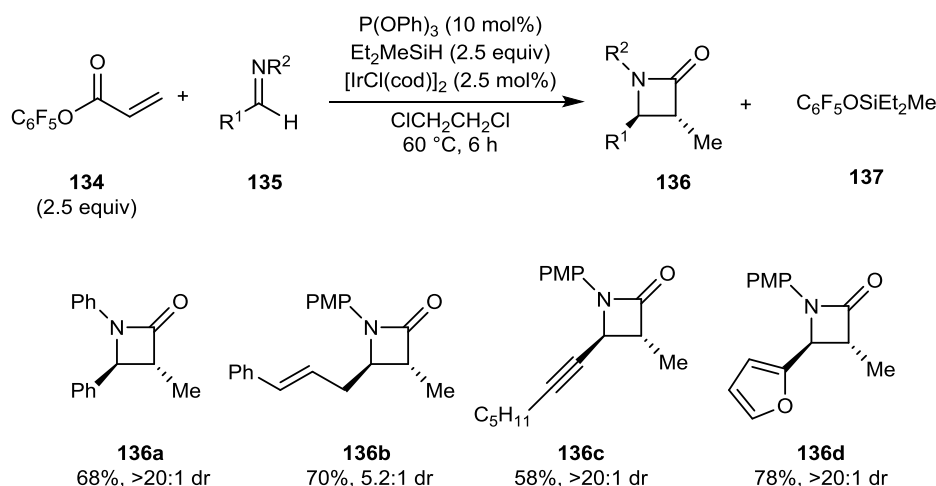
In 2002, Matsuda and co-workers reported a rhodium-catalysed method for the synthesis of β -amino esters from aldimines, methyl acrylate and diethylmethylsilane (Scheme 1.45).⁵⁵



Scheme 1.45: Rh-Catalysed Mannich-type Reaction of Aldimine with Methyl Acrylate⁵⁵

In the presence of rhodium catalyst $[\text{Rh}(\text{cod})(\text{P}(\text{OPh})_3)_2]\text{OTf}$, diethylmethylsilane as reductant in CH_2Cl_2 furnished Mannich-type products **133a-133c**, in high yields and moderate diastereoselectivities. The reaction was intolerant of *N*-alkyl aldimines, such as *N*-cyclohexyl aldimine **132d**, which did not react to give β -ester **133d** under the given reaction conditions. Though a general highly diastereoselective method was not established, the report demonstrated a new route to design certain types of β -amino carbonyl compounds under almost neutral conditions.

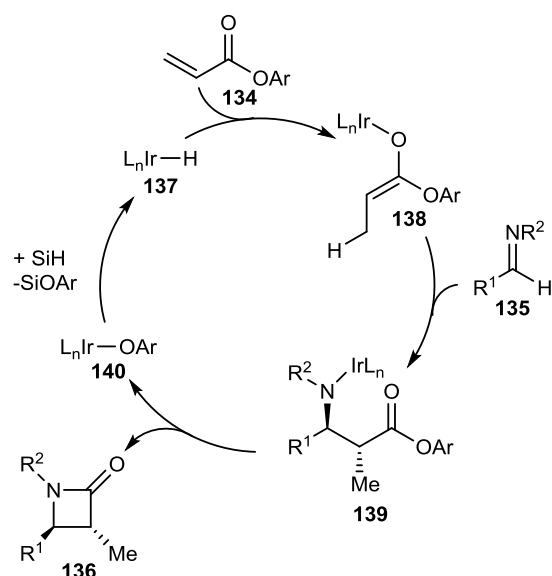
In the same year, Morken and co-workers reported a highly diastereoselective iridium-catalysed reductive coupling of acrylates **134** and imines **135** in the synthesis of trans β -lactams **136a-136d** (Scheme 1.46).⁵⁷ β -Lactams are prevalent substructures in biologically active compounds such as effective antibiotic agents, protease inhibitors and cholesterol absorption inhibitors, therefore their synthesis is of significant value.⁵⁸



Scheme 1.46: Iridium-Catalysed Synthesis of β -Lactams⁵⁷

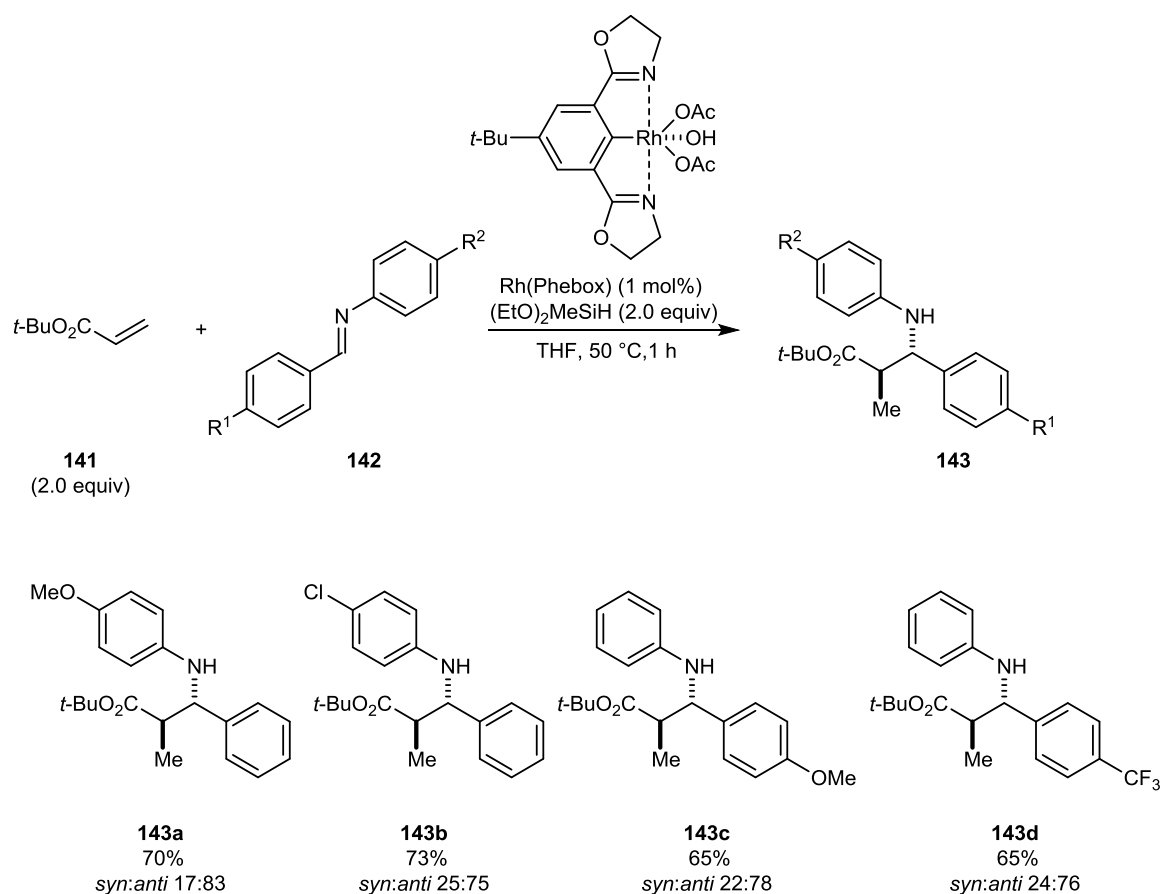
C-aryl imines furnished the corresponding β -lactams **136a** in good yields and high diastereoselectivities. Allylic and propargylic imines reacted without competitive hydrosilation of the C-C π -bond affording products **136b** and **136c** respectively. They also demonstrated that furans do not interfere with the reaction (product **136d**).

A postulated reaction mechanism was included in the communication (Scheme 1.47). The first step involves the *in situ* generation of an iridium hydride **137** which reacts with the acrylate **134** to provide an iridium enolate **138**. Iridium enolate **138** couples with aldimine **135** to provide a β -amido ester **139**. Subsequent cyclisation furnishes the β -lactam **136** and an iridium phenoxide **140**.



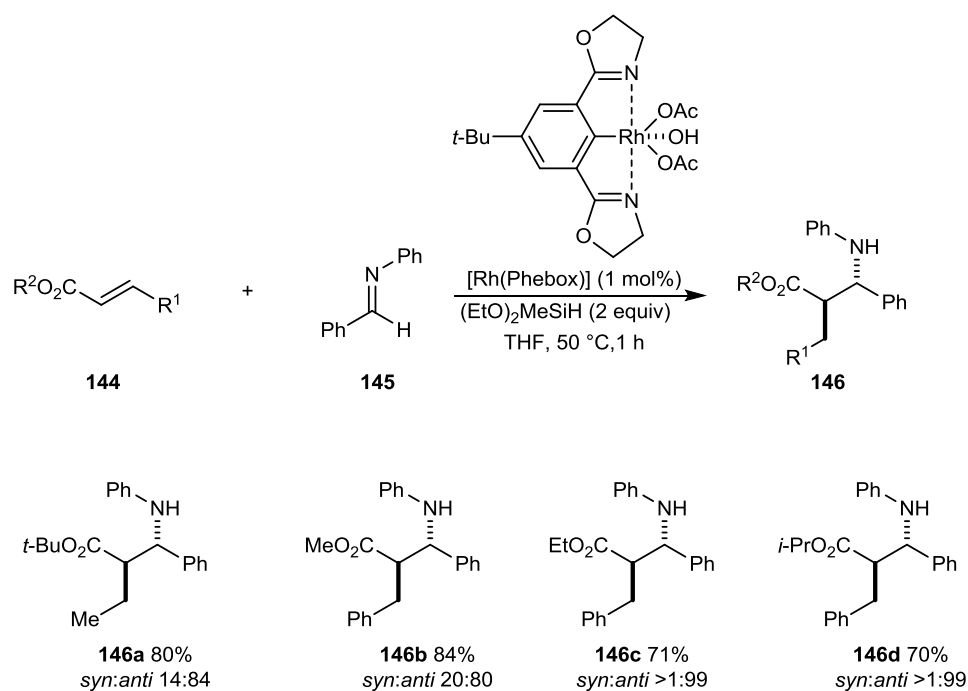
Scheme 1.47: Postulated Reaction Mechanism of Iridium-Catalysed Synthesis of β -Lactams⁵⁷

A report by Nishiyama and co-workers in 2007, demonstrated the conjugate reduction of α,β -unsaturated esters followed by a Mannich-type coupling towards aldimines using a rhodium-bis(oxazolinyl)phenyl Rh(Phebox) catalyst and alkoxyhydrosilanes to give β -amino esters **143a-143d** (Scheme 1.48).⁵⁹ Good yields and high *anti*-selectivity were observed in all cases and electron-withdrawing and electron-donating substituents were tolerated on both aryl groups.



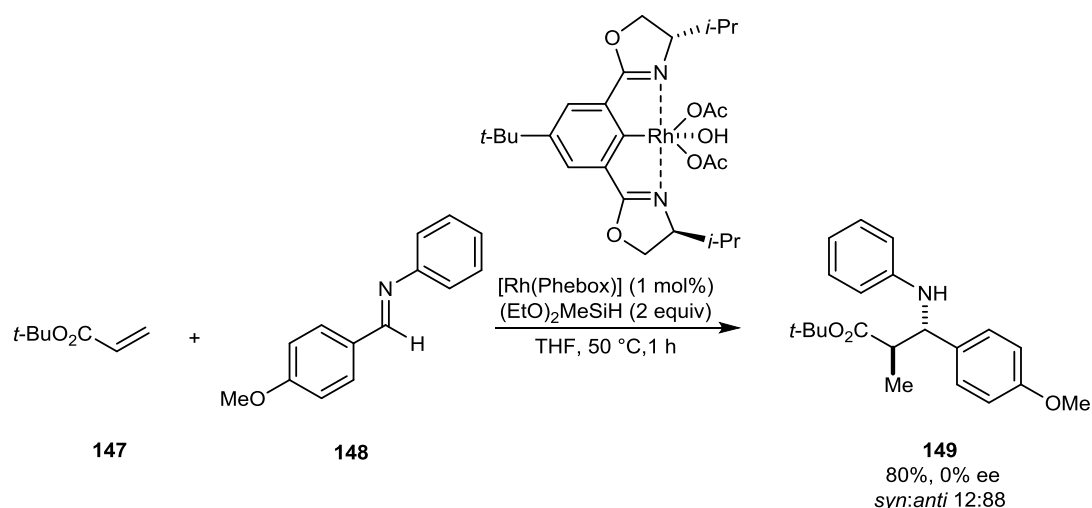
Scheme 1.48: Reductive Mannich-Type Coupling of Aldimines and *t*-Butyl Acrylate⁵⁹

Crotonates and cinnamates were also explored as enolate sources giving products with good yields and diastereoselectivities (Scheme 1.49). Interestingly, it was found that ethyl and *iso*-propyl cinnamates gave exclusively the *anti*-isomer (products **146c-146d**).



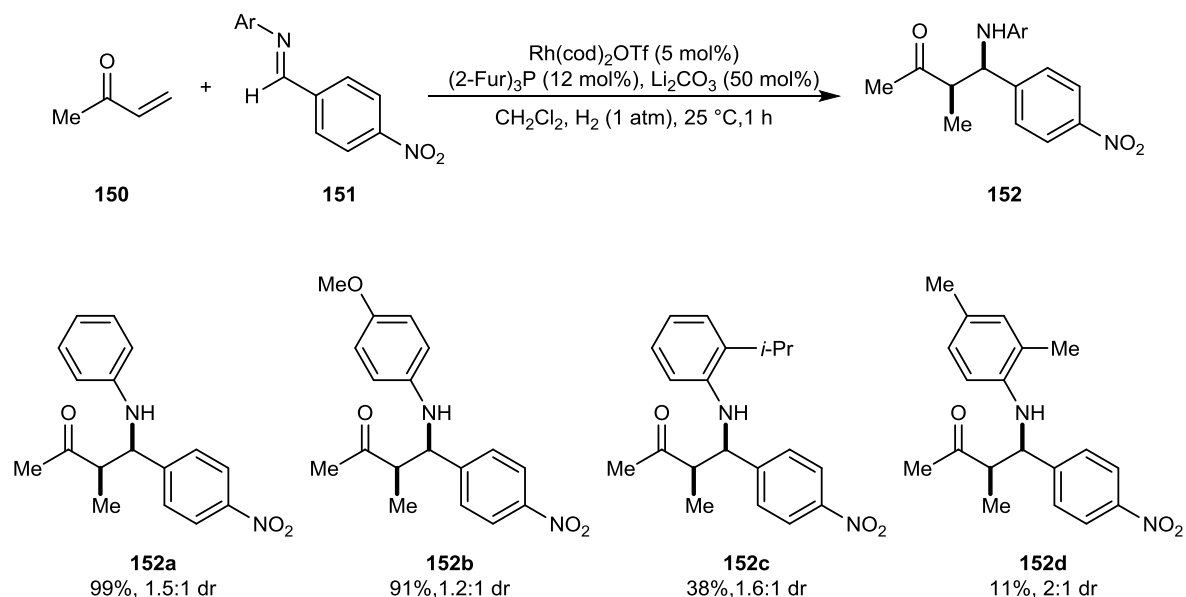
Scheme 1.49: Reductive Mannich-type Coupling of Aldimines with Crotonates and Cinnamates⁵⁹

An attempt at asymmetric induction was unsuccessful. Employing a chiral Rh(Phebox) catalyst, the reaction of *p*-methoxyimine **148** with *tert*-butyl acrylate (**147**) gave Mannich adduct **149** in high yield and diastereoselectivity; however, no enantioselectivity was observed (Scheme 1.50).



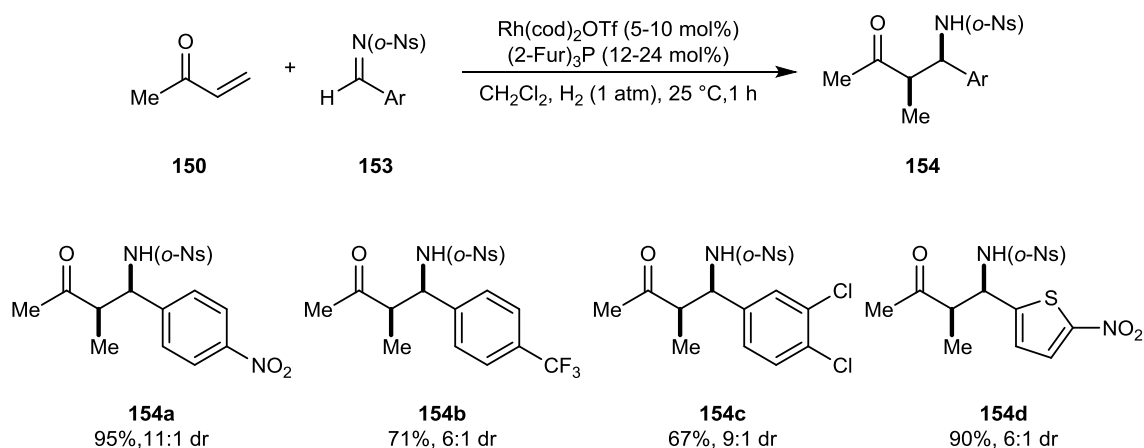
Scheme 1.50: Asymmetric Attempt at Reductive Mannich-Type Coupling of Aldimines with *tert*-Butyl Acrylate⁵⁹

In 2007, Krische and co-workers reported a rhodium-catalysed reductive Mannich coupling of vinyl ketones to *N*-sulfonylimines mediated by hydrogen. Initial studies focused on the hydrogenative coupling of methyl vinyl ketone (MVK) to *N*-arylaldimines (Scheme 1.51).⁶⁰



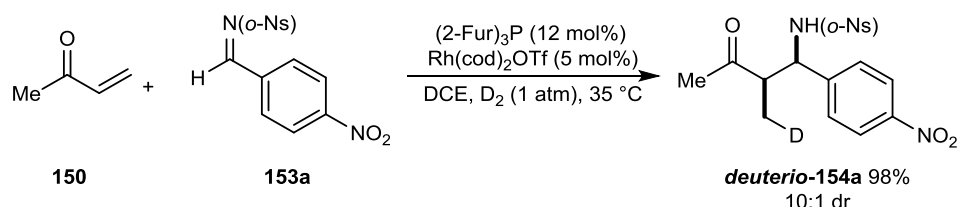
Scheme 1.51: Hydrogen Mediated Reductive Mannich Coupling of MVK to *N*-Arylaldimines⁶⁰

They reported that the coupling of MVK to imine **151a** derived from aniline gave the desired reductive Mannich product **152a** in excellent yield but poor diastereoselectivity. They postulated aldimines which incorporated more sterically demanding groups may couple with higher levels of diastereoselection. Accordingly, sterically hindered imines were examined which incorporated *o*-isopropylphenyl and *o,p*-dimethylphenyl *N*-aryl residues. Increased steric demands did not result in heightened levels of diastereoselection and affected conversion adversely (products **152c** and **152d**). It was reasoned that the poor levels of diastereoselection in additions to *N*-arylaldimines were due to facile geometrical isomerism in the presence of the metal catalyst.⁶¹ Hydrogenative Mannich coupling proceeded more efficiently with highly electrophilic *N*-(*o*-nitrobenzenesulfonyl)aldimines **153** to afford the coupling products **154a-154d** in good to excellent yields and superior diastereoselectivities compared with aniline derived imines **151** (Scheme 1.52). Higher catalyst loadings were required (10 mol%) for good conversions.



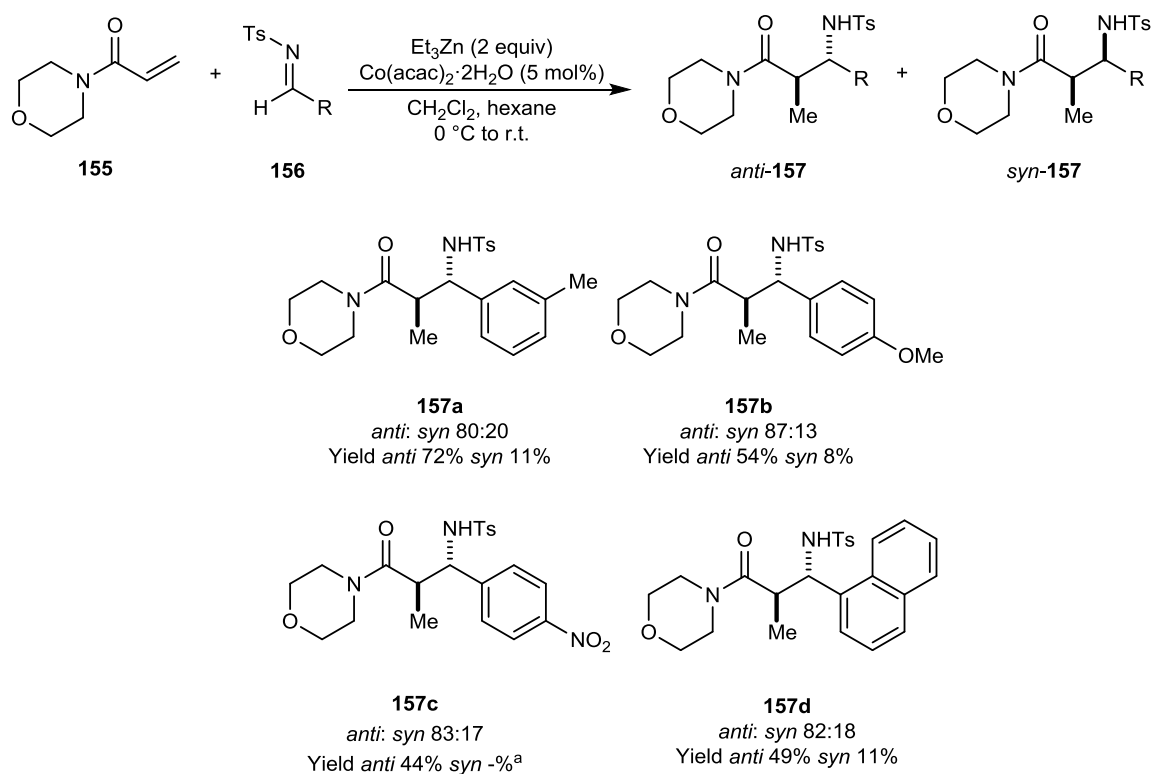
Scheme 1.52: Diastereoselective Hydrogen-Mediated Reductive Mannich Coupling of MVK to *N*-(*o*-Nitrophenyl)sulfonylaldimines⁶⁰

Deuterium experiments were conducted to investigate the mechanism of the reaction (Scheme 1.53). Performing the reductive coupling reaction using MVK **150**, *p*-nitrobenzalimine (**153a**) and elemental deuterium, they found the Mannich coupling product *deuterio*-**154a** incorporates a single deuterium atom at the former enone β -position and incorporation at the α -position is not observed. The sole incorporation of a deuterium atom is consistent with a mechanism involving irreversible enone hydrometalation. However, enone-imine oxidative coupling followed by hydrogenolytic cleavage of the resulting oxarhodacycle cannot be excluded.



Scheme 1.53: Reductive Mannich Coupling under a Deuterium Atmosphere⁶⁰

Lam and co-workers reported a new variant of the reductive Mannich reaction involving the coupling of commercially available 4-acryloylmorpholine (**155**) with a range of aromatic *N*-tosyl aldimines **156** using diethylzinc as the stoichiometric reductant and a cobalt salt as the precatalyst (Scheme 1.54).⁶²

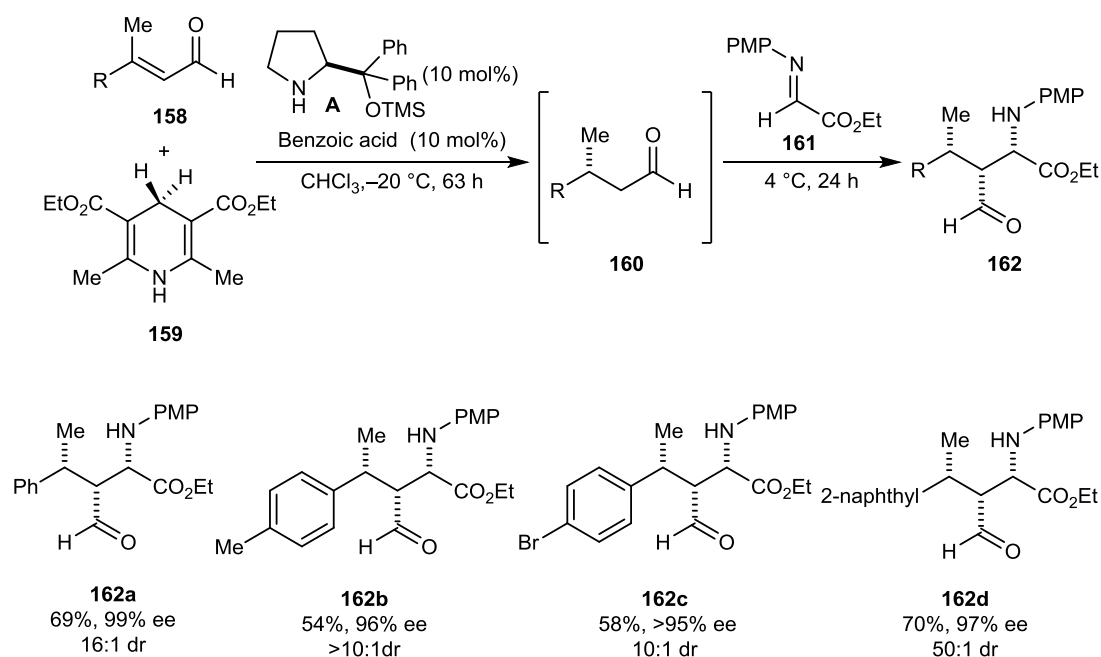


^a The *syn*-Mannich product could not be isolated in pure form

Scheme 1.54: Cobalt-Catalysed Reductive Mannich Reaction of 4-Acrylmorpholine with *N*-Tosyl Aldimines⁶²

N-Tosyl aldimines were found to undergo reductive coupling with 4-acrylmorpholine (**155**) in moderate to good yields and with good levels of diastereoselection. Aldimines with electron-donating substituents such as methyl and methoxy (products **157a-157b**) provided superior results compared with those containing electron-withdrawing substituents (product **157c**).

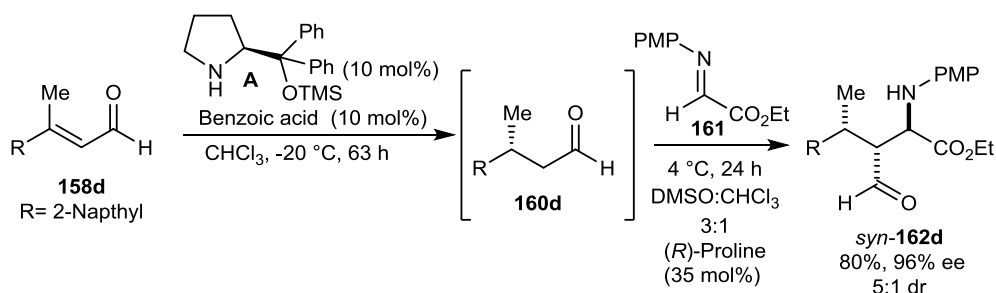
Cordova and Zhao reported an amine-catalysed direct asymmetric reductive Mannich reaction of β,β -disubstituted α,β -unsaturated aldehydes **158** furnishing amino acid products containing three contiguous stereocenters (Scheme 1.55).⁵⁶



Scheme 1.55: Direct Catalytic Enantioselective Reductive Mannich-type Reaction⁵⁶

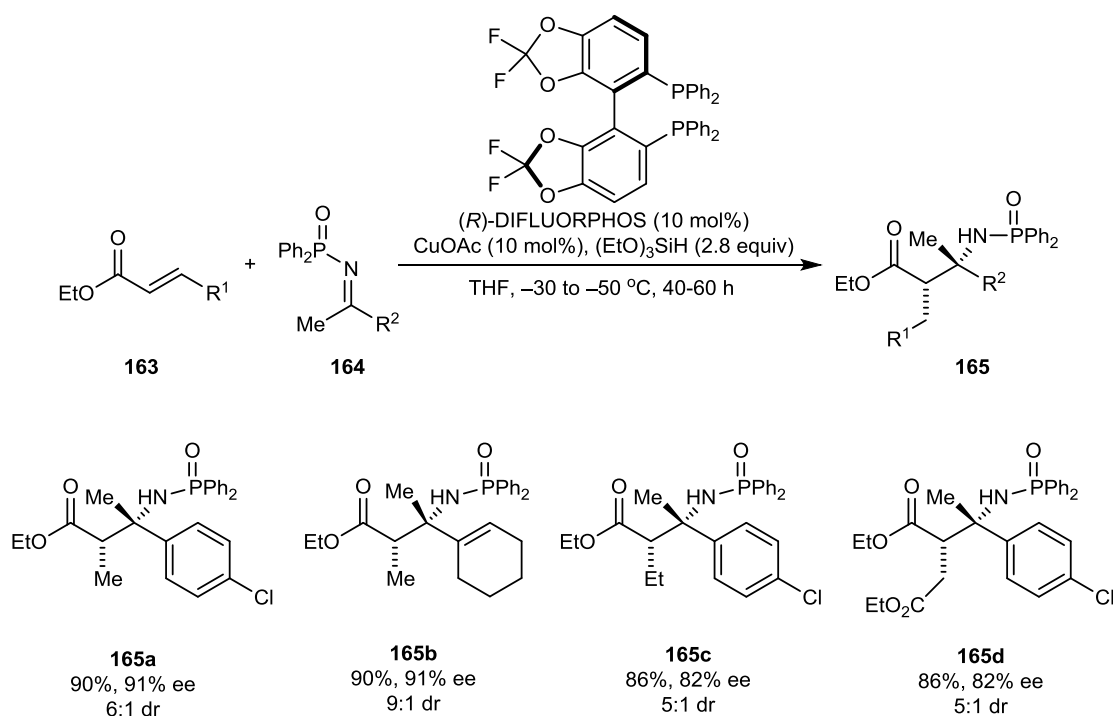
In the presence of chiral pyrrolidine **A** with Hantzsch ester (**159**) as hydride source, the reaction proceeded smoothly to furnish the corresponding chiral aldehydes **160** in good to high yields and excellent *ee*'s (up to 97%). Employing *N*-PMP-protected α -iminoglyoxylate (**161**) as the electrophile the reductive Mannich-type reaction provided the corresponding amino acid derivatives **162a-162d** in good yields and with good to excellent diastereo- and enantioselectivity.

An organocatalytic enantioselective reductive Mannich protocol was also developed which led to the other diastereomer of **162d**. A catalytic amount of (*R*)-Proline was added to the reaction mixture together with *N*-PMP-protected α -imino-glyoxylate (**161**) and a *syn*-selective Mannich addition (product **162d**) was achieved with high enantioselectivity in a one-pot reaction (Scheme 1.56).



Scheme 1.56: Syn-Selective Reductive Mannich-type Reaction using (*R*)-Proline⁵⁶

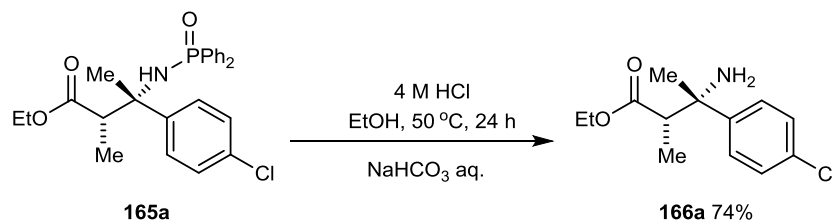
In 2008, Shibasaki *et al.* developed the first CuH-catalysed asymmetric reductive Mannich reaction employing *N*-phosphinoyl ketimines. This methodology was the first example of the catalytic asymmetric synthesis of β -amino acid derivatives (Scheme 1.57).⁶³



Scheme 1.57: Catalytic Asymmetric Reductive Mannich Reaction of Ketimines⁶³

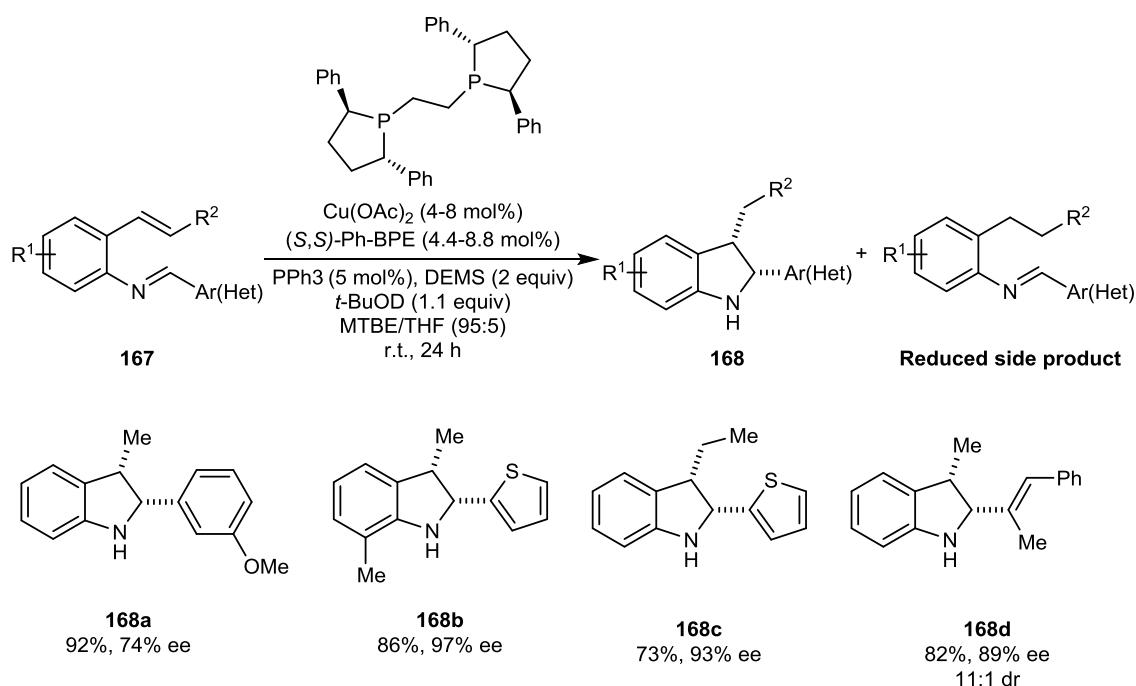
Exchanging the stoichiometric reducing agent from pinacolborane for hydrosilanes improved the enantioselectivity significantly. Lower reaction temperatures and employing sterically less hindered bis-arylphosphines as ligands saw an improvement in the product yield. Using a CuOAc-DIFLUORPHOS complex catalyst and (EtO)₃SiH as a reducing agent at -30°C or lower, α,β -unsaturated esters and *N*-phosphinoyl ketimines proceeded efficiently to reductively couple in a

Mannich fashion. The substrate scope covers both aromatic and α,β -unsaturated ketimines as acceptors, affording α -methyl, ethyl-, and ethoxy-carbonylmethyl-substituted products (products **165a-165d** respectively) with high enantio- and diastereoselectivities. The products were converted to enantiomerically enriched β -amino acid derivatives **166a** in high yield without any racemisation or epimerisation through cleavage of the diphenylphosphino group under acidic conditions (Scheme 1.58).



Scheme 1.58: Conversion to β -Amino Acid Derivative⁶³

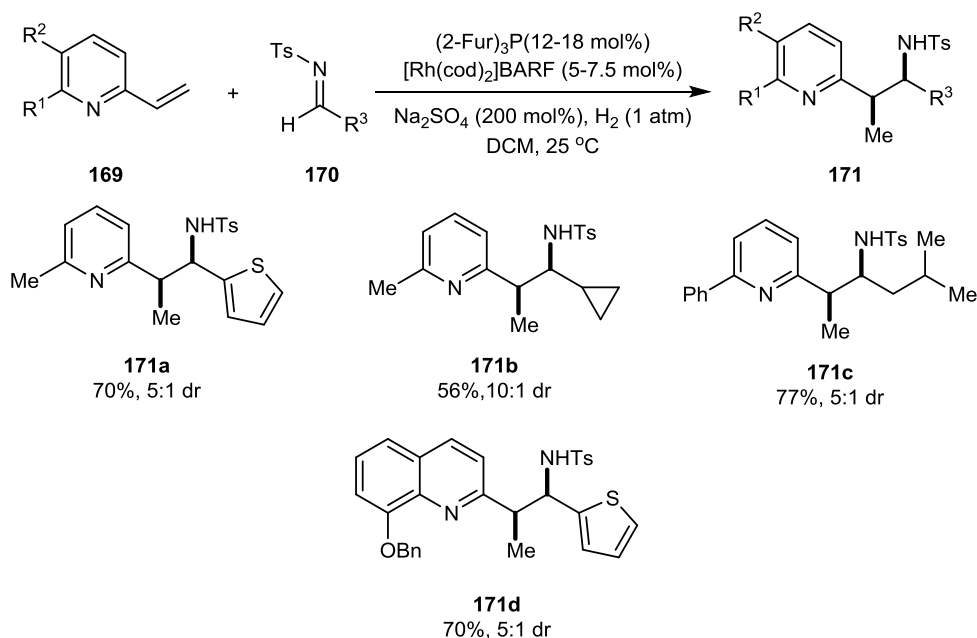
Recently, Buchwald and co-workers reported a CuH-catalysed method for the preparation of highly functionalised indolines (Scheme 1.59).⁶⁴



Scheme 1.59: Enantioselective CuH-Catalysed Synthesis of 2,3-Disubstituted Indolines⁶⁴

The reaction displayed good functional group tolerance and gave exclusively *cis*-indolines in high yields and good to excellent enantioselectivities (products **168a-168c**). The reasons for the observed diastereoselectivity were not disclosed in the communication. 2-Alkenylimine precursor **167d** which possesses a vinyl group, proved to be the only exception providing indoline **168d** with diminished diastereoselectivity (11:1 dr). Interestingly, the choice of alcohol was important for the yield. When *t*-BuOD was used in lieu of *t*-BuOH the reduced styrene side product was reduced (from 3% to <1%) and a slight increase in yield was obtained (from 92% to 96%). Extension of this method to β -substituted styrenes furnished indoline **168c** with good yield and high enantioselectivity; however, a higher catalyst loading was required (8 mol%) and the best result was obtained in the absence of triphenylphosphine.

To the best of our knowledge, the only report of catalytic reductive coupling reactions of alkenylazarenes is that from the Krische group, describing a racemic rhodium-catalysed hydrogenative coupling⁶⁵ of vinylazines with *N*-arylsulfonyl imines (Scheme 1.60).⁶⁶



Scheme 1.60: Reductive Coupling of 2-Vinyl Pyridines and Imines⁶⁶

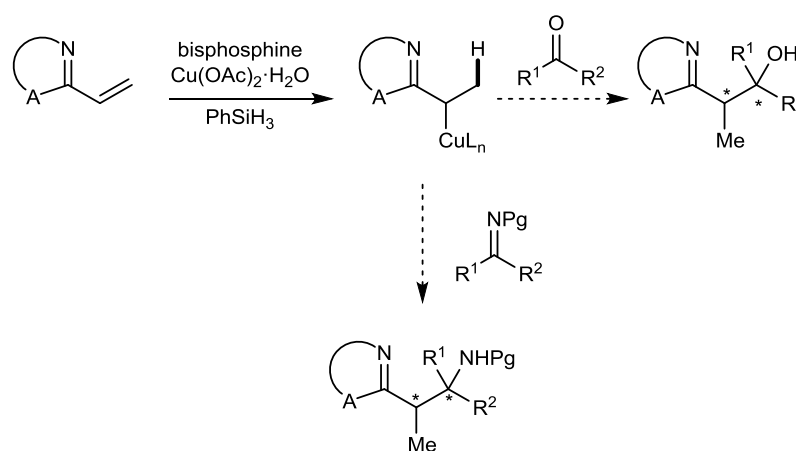
Catalytic hydrogenation of alkenylazines **169** and *N*-arylsulfonyl imines **170** in the presence of a cationic rhodium catalyst ligated by (2-Fur)₃P and molecular hydrogen results in the reductive coupling to furnish branched products of imine addition **171a-171d** with modest levels of *syn*-diastereoselectivity. The reaction proceeds efficiently at ambient temperatures and pressures. In evaluating the scope of the vinyl azine partner, they noted that the parent 2-vinylpyridine did not participate in the coupling, most likely due to strong coordination at nitrogen to the rhodium catalyst rendering it ineffective. Accordingly, 6-substituted vinylpyridines were selected as coupling substrates and participated efficiently to (hetero)aromatic (products **171a** and **171d**) and aliphatic imines (products **171b** and **171c**). Fused bicyclic vinyl azines were also effective coupling partners (product **171d**).

The results in Krische's paper are impressive; however, there are some limitations within their work. We envisaged that a related enantioselective variant employing chiral copper hydride chemistry could be developed.

1.4 Conclusion

To summarise, it has been shown that azaarenes are important moieties in natural products, pharmaceuticals and other biologically active molecules. The use of azaarenes as activating groups has been successfully employed in enantioselective catalysis with a number of reports in literature. It has been demonstrated that 2-alkenylazaarenes can act as activators of an adjacent olefin in the electrophilic component of the reaction and provide Michael addition products with excellent diastereo- and enantioselectivities. With this knowledge in hand, the aim of our research was to extend current methodologies and to develop other complementary novel methods for the asymmetric functionalisation of azaarenes.

In the following results and discussion sections, studies exploiting the electron-withdrawing ability of a C=N embedded within an azaarene to couple with ketones and imines in the construction of chiral tertiary alcohol and chiral amines are discussed (Scheme 1.24).

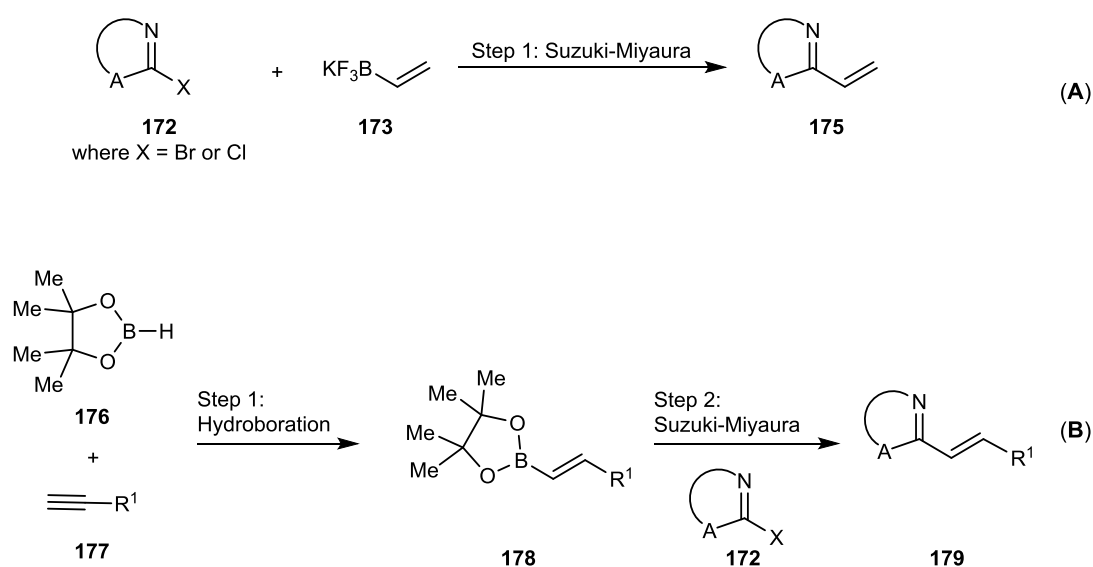


Scheme 1.24: Catalytic CuH-Catalysed Reductive Couplings

2. ENANTIOSELECTIVE REDUCTIVE COUPLING OF ALKENYLAZAARENES WITH KETONES

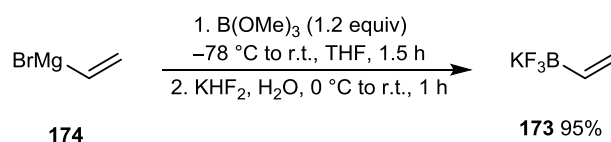
2.1 Preparation of 2-Alkenylazaarenes

For the preparation of 2-vinylazaarenes and β -substituted alkenylazaarenes, the most simple and efficient method involves a Suzuki-Miyaura coupling between a halogenated azaarene **172** and potassium vinyltrifluoroborate (**173**) or an alkenylboronic ester **178** (Scheme 2.01).



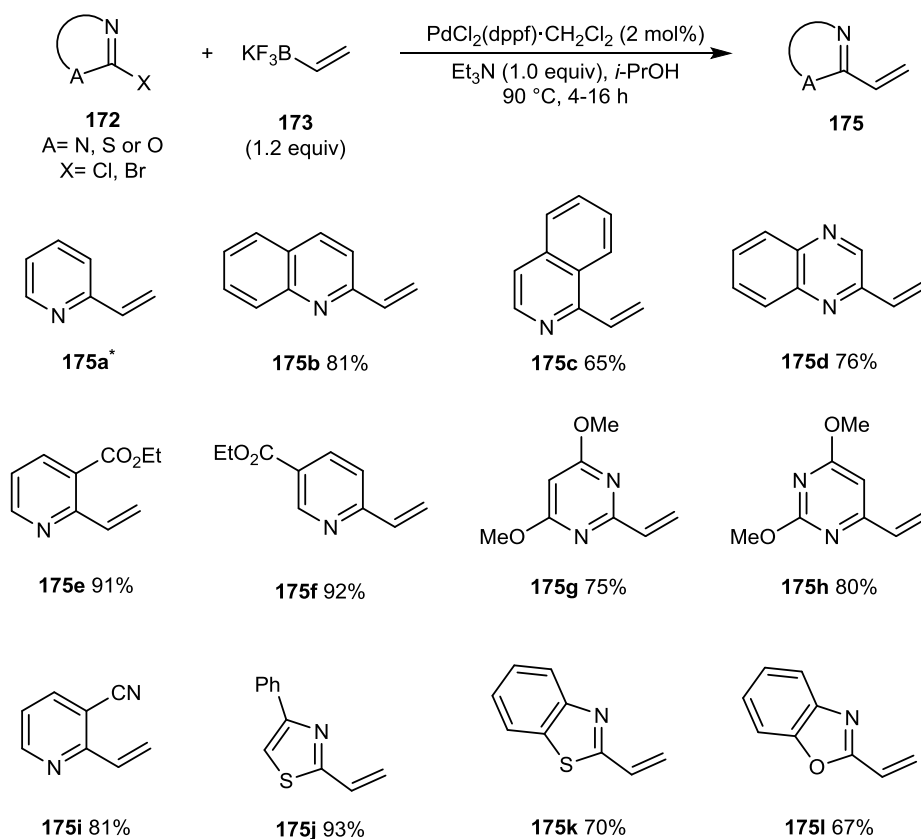
Scheme 2.01: Preparation of Alkenylazaarenes via Suzuki-Miyaura Cross-Coupling Chemistry

Although potassium vinyltrifluoroborate (**173**) is commercially available, it was prepared in a one-step procedure through addition of vinyl magnesium bromide (**174**) to trimethyl borate and *in situ* treatment of the resulting boronic ester with KHF_2 (Scheme 2.02).



Scheme 2.02: Synthesis of Potassium Vinyltrifluoroborate

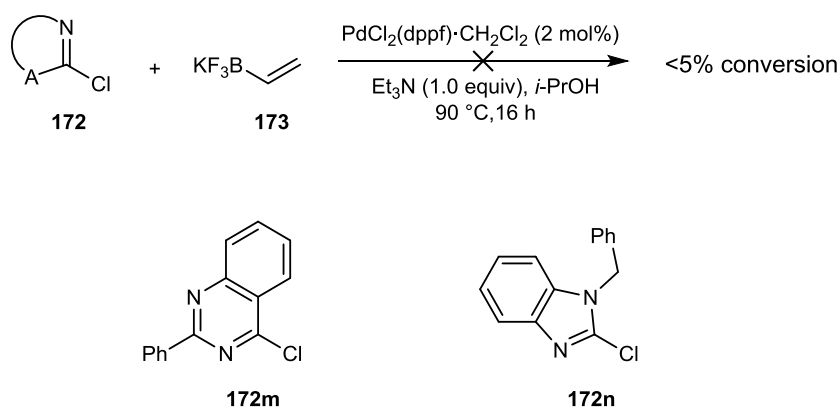
2-Vinylazaarenes **175** were synthesised using Suzuki-Miyaura cross-coupling reactions conditions developed by Molander and co-workers.⁶⁷ Halogenated azaarenes **172** were coupled with potassium vinyltrifluoroborate (**173**) in the presence of Et₃N and catalytic PdCl₂(dppf)·CH₂Cl₂ to give a range of 2-vinylazaarenes **175b-175l** in good to high yields (Scheme 2.03).



* Reagent purchased from commercial sources

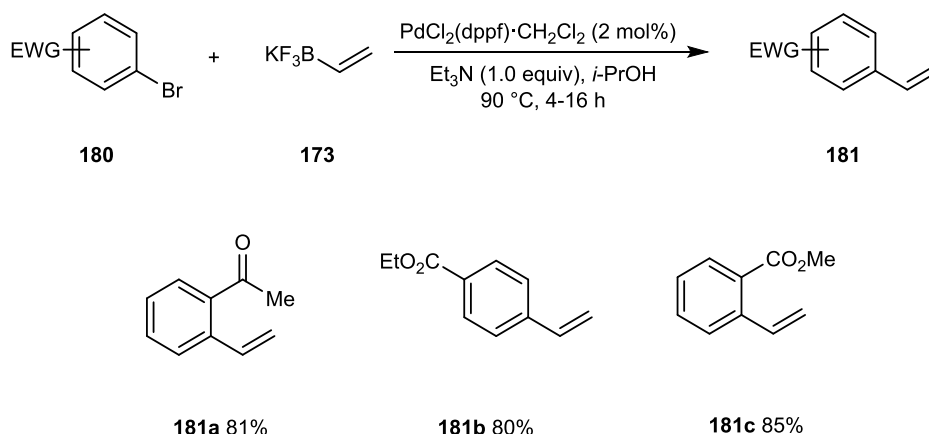
Scheme 2.03: Preparation of Alkenylazaarenes via Suzuki-Miyaura Cross-Coupling Chemistry

Attempts to synthesise sterically hindered 2-vinylazaarenes containing phenyl groups were unsuccessful; bulky halo-azaarenes **172m** and **172n** did not undergo cross-coupling efficiently with potassium vinyltrifluoroborate under the standard conditions (Scheme 2.04). Analysis of the ¹H NMR spectra of the crude reaction mixtures showed <5% conversion to the coupled product and the starting material remained primarily unreacted.



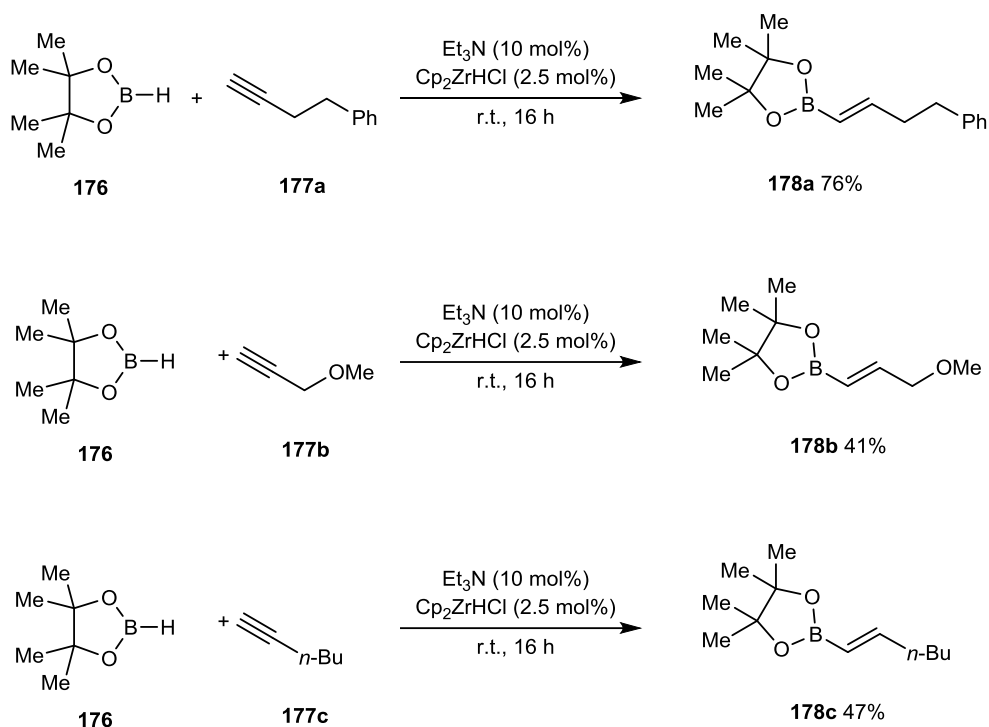
Scheme 2.04: Unsuccessful Substrate Preparation

Additionally, various 2-vinylarenes containing electron-withdrawing substituents were prepared in high yields (**190a-190c**) using the general Suzuki-Miyaura cross-coupling procedure (Scheme 2.06).⁶⁷ Drawing on knowledge from a previous study within the Lam group on rhodium-catalysed 1,4-arylations,^{10f} it was hoped that electron-deficient vinylarenes may also participate in a copper-catalysed reductive coupling reaction.



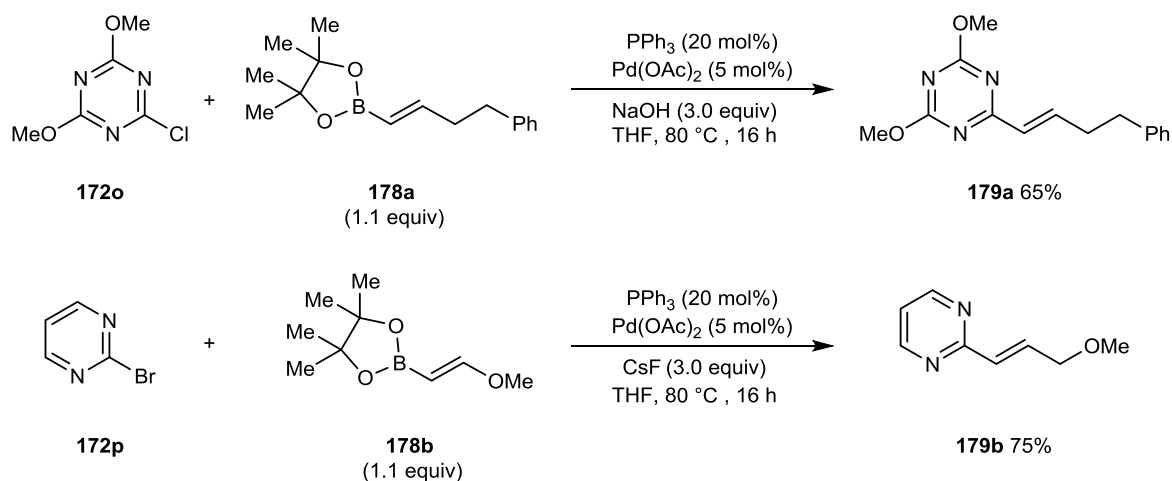
Scheme 2.05: Synthesis of Vinylarenes

The preparation of β -substituted alkenylazaarenes involved a two-step strategy. First, alkenylboronic esters **179** were synthesised following a procedure previously developed by Wang and co-workers.⁶⁸ This reaction involves the zirconium-mediated hydroboration of terminal alkynes **177** leading to the stereoselective production of *E*-alkenylboronic esters **178a-178c** in good to modest yields (Scheme 2.06).



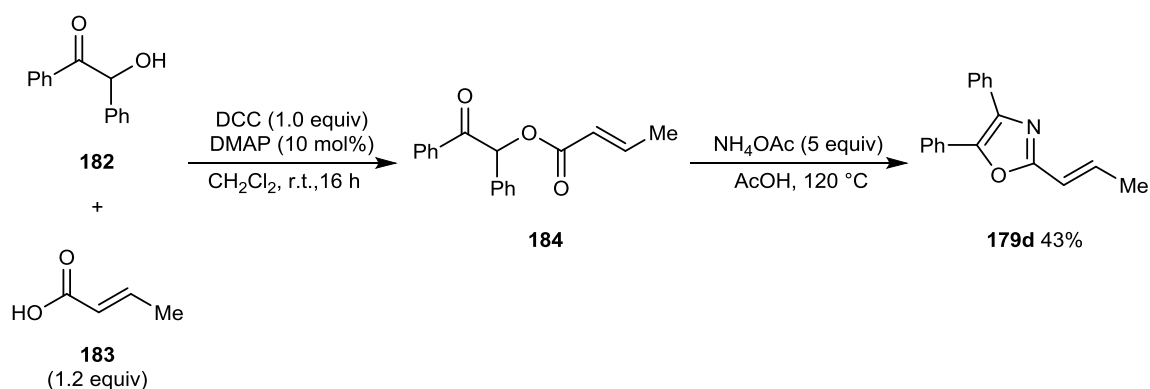
Scheme 2.06: Synthesis of Alkenylboronic Esters

The newly synthesised alkenylboronic esters **178** were then subjected to the Suzuki-Miyaura cross-coupling procedure with halogenated azaarenes **172** (Scheme 2.07). The reactions proceeded efficiently and β -substituted alkenylazaarenes **179a-179c** were isolated in good yields.



Scheme 2.07: Synthesis of β -Substituted Alkenylazaarenes

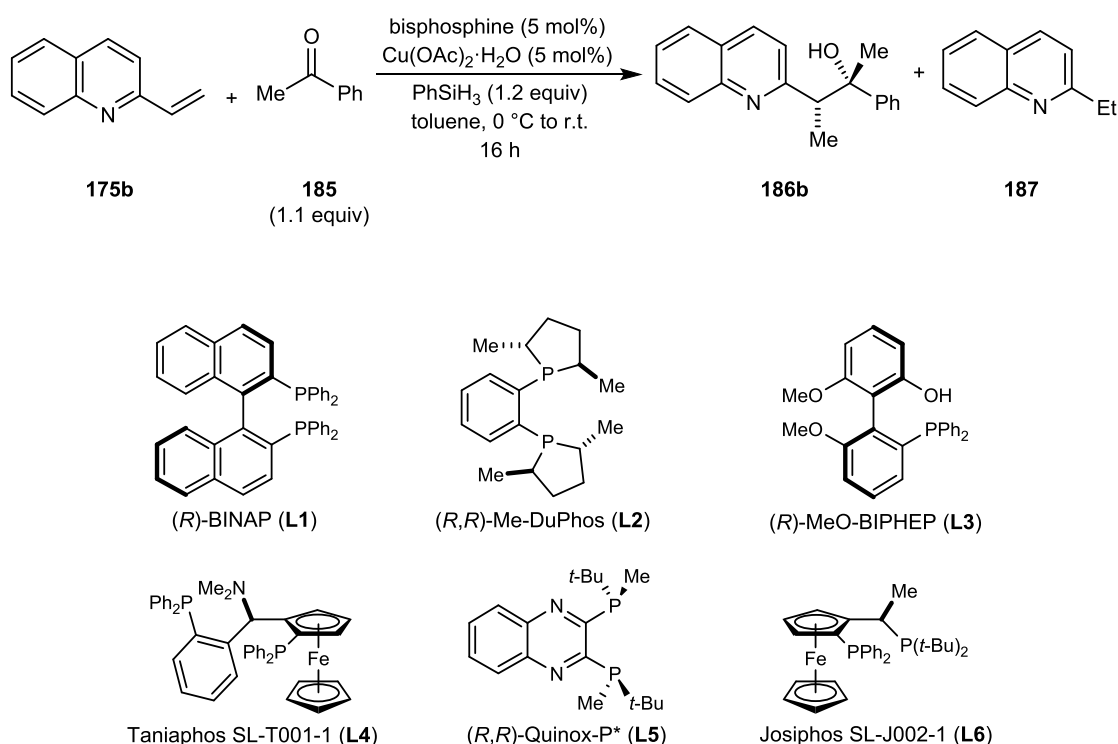
An alternative method to prepare β -substituted alkenylazaarenes involved direct formation of the azaarene moiety. The reaction of benzoin (**182**) with crotonic acid (**183**) in the presence of DMAP and DCC afforded intermediate **184**, which upon treatment with ammonium acetate in glacial acetic acid cyclised to give alkenyloxazole **179d** in high yields (Scheme 2.08).



Scheme 2.08: Synthesis of β -Substituted 2-Alkenyloxazole

2.2 Enantioselective Copper-Catalysed Reductive Coupling of Alkenylazaarenes with Ketones

The project began with a screening of chiral bisphosphines in order to obtain the optimum ligand for this enantioselective copper-catalysed reductive coupling process. For the ligand evaluation, 2-vinylquinoline (**175b**) was selected as the azaarene substrate and commercially available acetophenone (**185**) was selected as the ketone coupling partner. Drawing on knowledge from a related study on copper-catalysed reduction of β,β -disubstituted alkenylazaarenes,^{10h} PhSiH_3 was selected as the hydride source, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ as the source of copper and toluene as the solvent. Under these conditions, various chiral bisphosphine ligands were screened (Table 2.01).

Table 2.01: Ligand Optimisation for Cu-Catalysed Reductive Coupling Reactions^a

Entry	Ligand	186b : 187 ^b	dr ^b	ee ^c (%)
1	L1	11:1	1:1	43, 50
2	L2	24:1	1:1	27, 17
3	L3	13:1	1:1	67, 67
4	L4	7:1	5:1	93, 60
5	L5	17:1	1:1	-60, 92
6	L6	12:1	1:1	92, 93

^aReactions were conducted using 0.1 mmol of **175b**. ^bDetermined by ¹H NMR analysis of the unpurified reaction mixtures. ^cDetermined by chiral HPLC analysis.

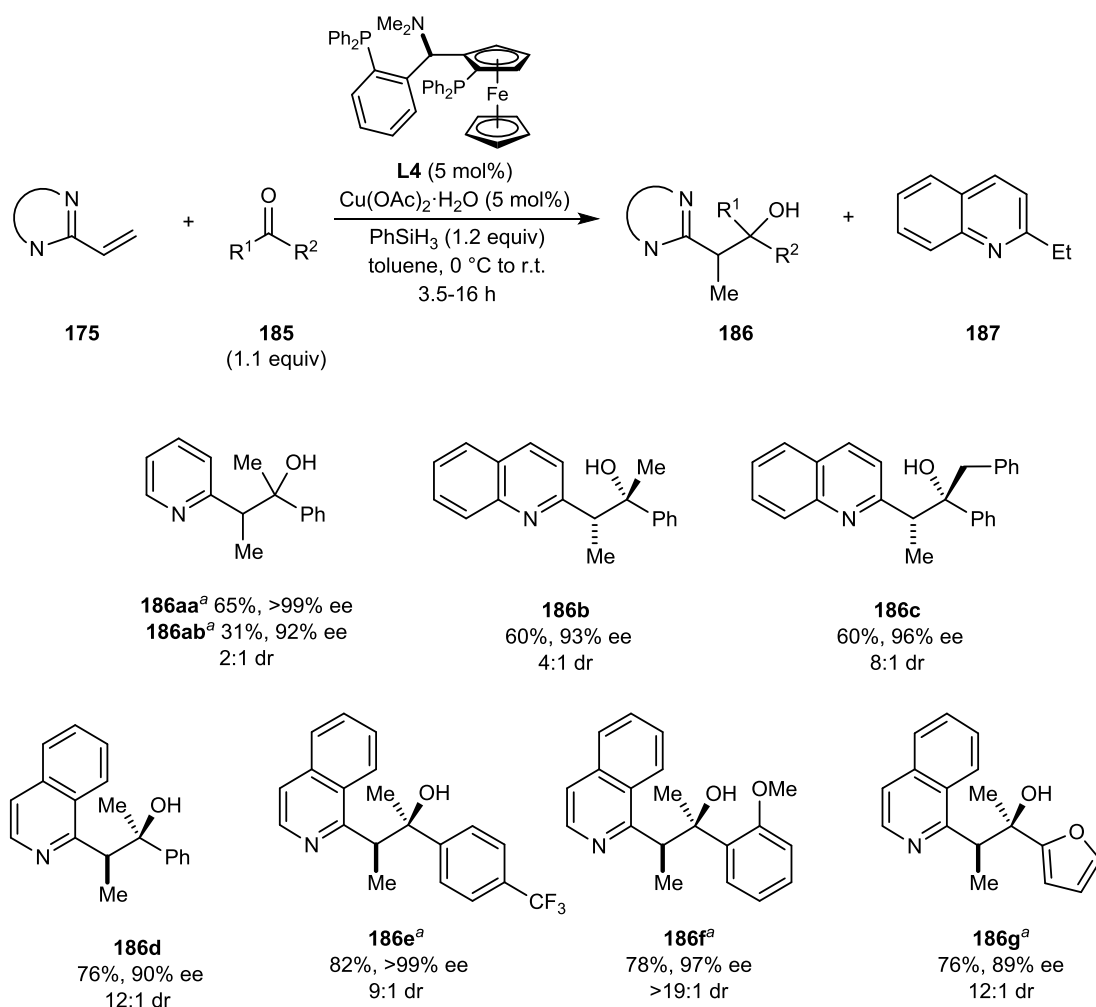
Proof of concept was quickly established, and all ligands evaluated led to complete consumption of 2-vinylquinoline to provide the coupling product **186b** as a mixture of diastereomers, along with traces of the reduction product **187**. Enantioselectivities were low with (*R*)-BINAP (**L1**) and (*R*)-MeO-DuPhos (**L2**). However, improved results were observed using (*R*)-MeO-Biphep (**L3**) with a modest enantioselectivity (67% *ee*). Superior enantioselectivities were obtained employing the Taniaphos ligand (**L4**), (*R,R*)-Quinox-P* **L5**, and the Josiphos ligand **L6**, and all provided *ee*'s above 90%. However, diastereoselectivity was only observed in the reaction

employing **L4**, which provided **186b** in 5:1 dr and 93% *ee* for the major isomer while also displaying good chemoselectivity between the coupling product and the reduction product (ratio **186b**:**187**). The excellent selectivity provided by **L4** prompted the selection of this ligand for further experimentation.

A screening of hydrosilanes revealed PhSiH_3 to be the optimum stoichiometric hydride for this reaction. Comparable enantioselectivities were observed with TMDS, PMHS and Ph_2MeSiH but reaction rates were slower.

In regard to the solvent choice, a range of polar and non-polar solvents including acetone, diethyl ether, dichloromethane and dioxane afforded reductive coupling product **186b** with decreased diastereoselectivity compared with toluene. Accordingly, toluene was selected as the preferred solvent for this process.

With a generalised procedure in hand, the scope of the reaction was investigated utilising the previously prepared 2-alkenylazaarenes. First, the scope of various 2-vinylazaarenes against acyclic ketones was tested (Scheme 2.09).



Unless stated otherwise, yields are of pure isolated major diastereomers

^a Reaction performed by Aakarsh Saxena

Scheme 2.09: Cu-Catalysed Reductive Aldol Coupling of Vinylazaarenes with Acyclic Ketones

2-Vinylpyridine coupled efficiently with acetophenone affording diastereomeric products **186aa** and **186ab** in high yields. These were obtained with high enantioselectivities (>99% and 92% *ee* respectively). Other compatible substrates included 2-vinylquinoline (products **186b** and **186c**) and 1-vinylisoquinoline (products **186d-186g**). The relative and absolute stereochemistries of quinoline-containing products **186b** and **186c** were determined by single crystal X-ray crystallography using a copper radiation source (Figure 2.01).⁶⁹

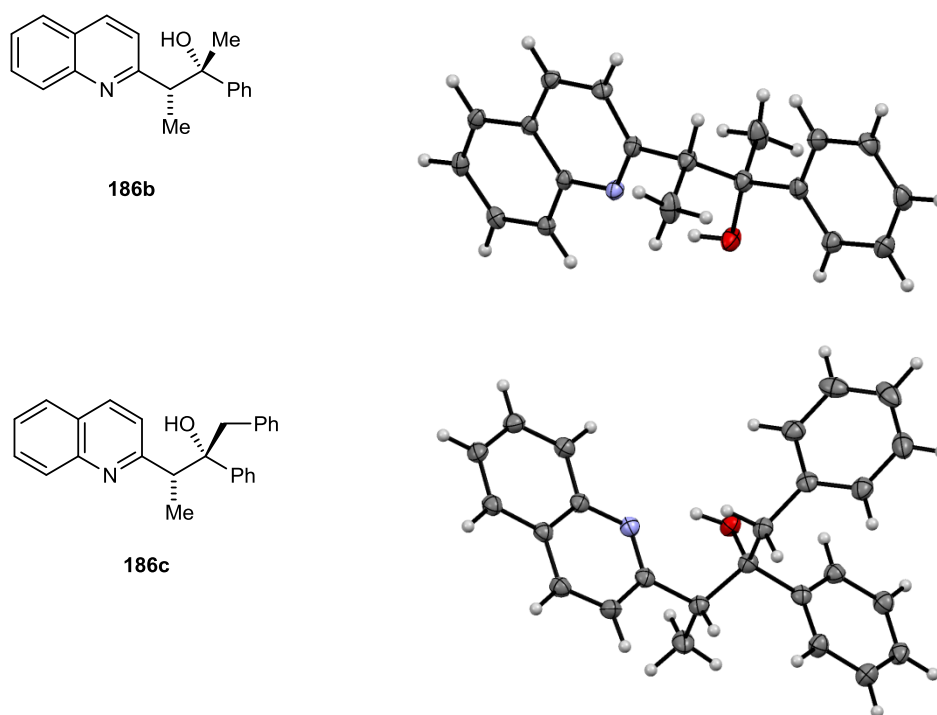
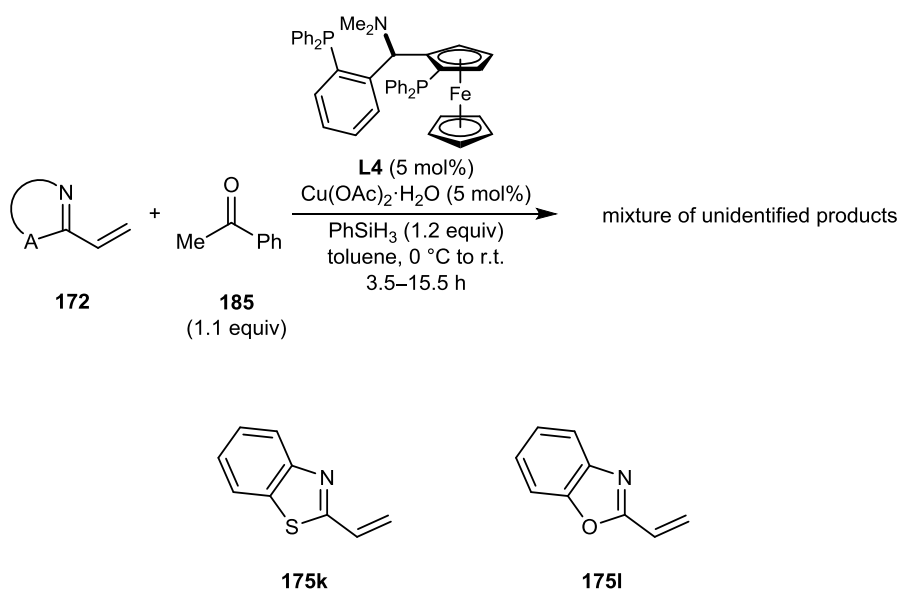


Figure 2.01: Stereochemical Determination of 2-Vinylquinoline-Containing Products

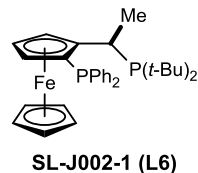
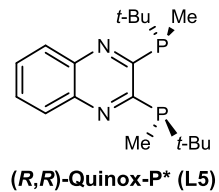
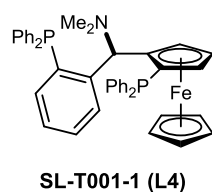
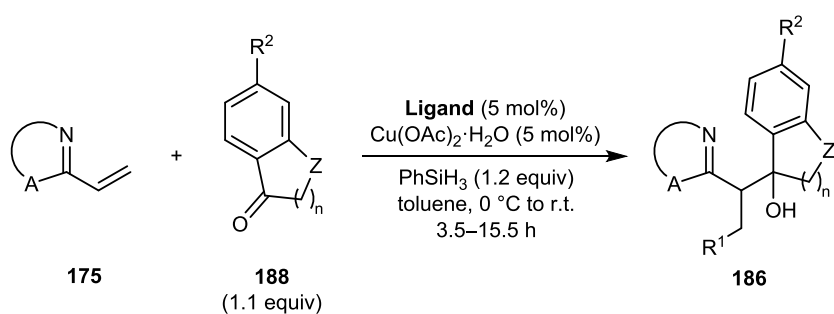
In regards to the reaction employing acyclic ketones, the diastereoselectivities of the reaction appeared to be dependent on the steric properties of the azaarene. Increasing diastereoselectivities were observed going from pyridine to quinoline to isoquinoline (compare diastereomeric ratios for products **186a**, **186b** and **186d**). The scope of the electrophile included acyclic ketones containing various alkyl, aryl or heteroaryl substituents (products **186a-186g**). Ketones with electron-withdrawing (product **186e**) and electron-donating (**186f**) groups on the aryl ring also coupled efficiently and with high enantioselectivities (up to >99% ee).

2-Vinylbenzothiazole (**175k**) and 2-vinylbenzoxazole (**175l**) did not undergo reductive coupling with acetophenone. ^1H NMR analysis of the unpurified reaction mixtures revealed a complex mixture of products and no peaks corresponding to either starting product or the desired product (Scheme 2.10). 2-Vinylbenzothiazole (**175k**) and 2-vinylbenzoxazole (**175l**) are not bench-stable and has a tendency to degrade at room temperature; therefore it is presumed that the rate of starting material decomposition is greater than the rate of reductive coupling under the standard conditions.

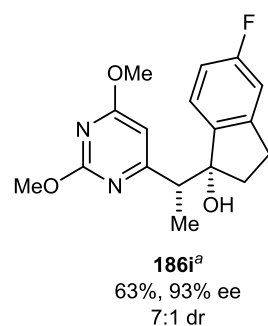
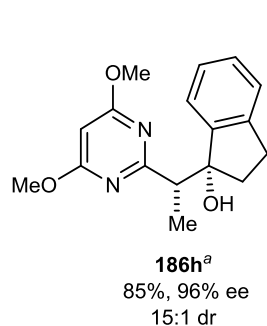


Scheme 2.10: Cu-Catalysed Reductive Aldol Coupling of Vinylazaarenes with Acyclic Ketones

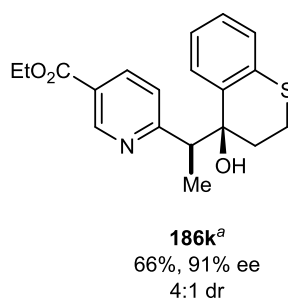
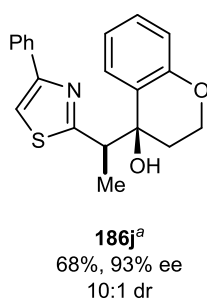
Deviating from acyclic ketones, five- and six-membered cyclic ketones were investigated by my co-worker Aakarsh Saxena. Cyclic ketones were also found to be effective substrates for the reductive coupling process (Scheme 2.11). This was demonstrated with two indanones (products **186h** and **186i**), 4-chromanone (product **186j**), 4-thiochromanone (product **186k**) and tetralone (product **186l**). Within these results, the scope of the azaarene was broadened to include two isomeric forms of pyrimidine (products **186h** and **186i**), a thiazole (**186j**), a 5-substituted pyridine (**186k**) and a quinoxaline (**186l**).



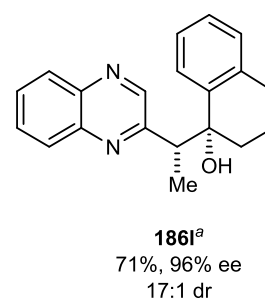
Using L4:



Using L5:



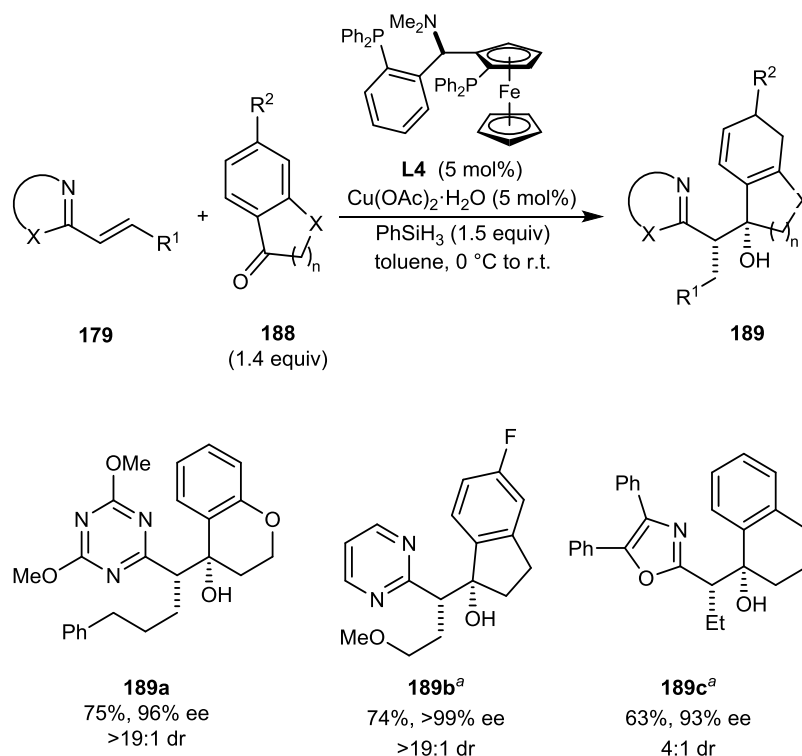
Using L6:



^a Reaction performed by Aakarsh Saxena

Scheme 2.11: Cu-Catalysed Reductive Aldol Coupling of Vinylazaarenes with Cyclic Ketones

Next, the scope of this reaction was extended to include β -substituted alkenylazaarenes (Scheme 2.12).



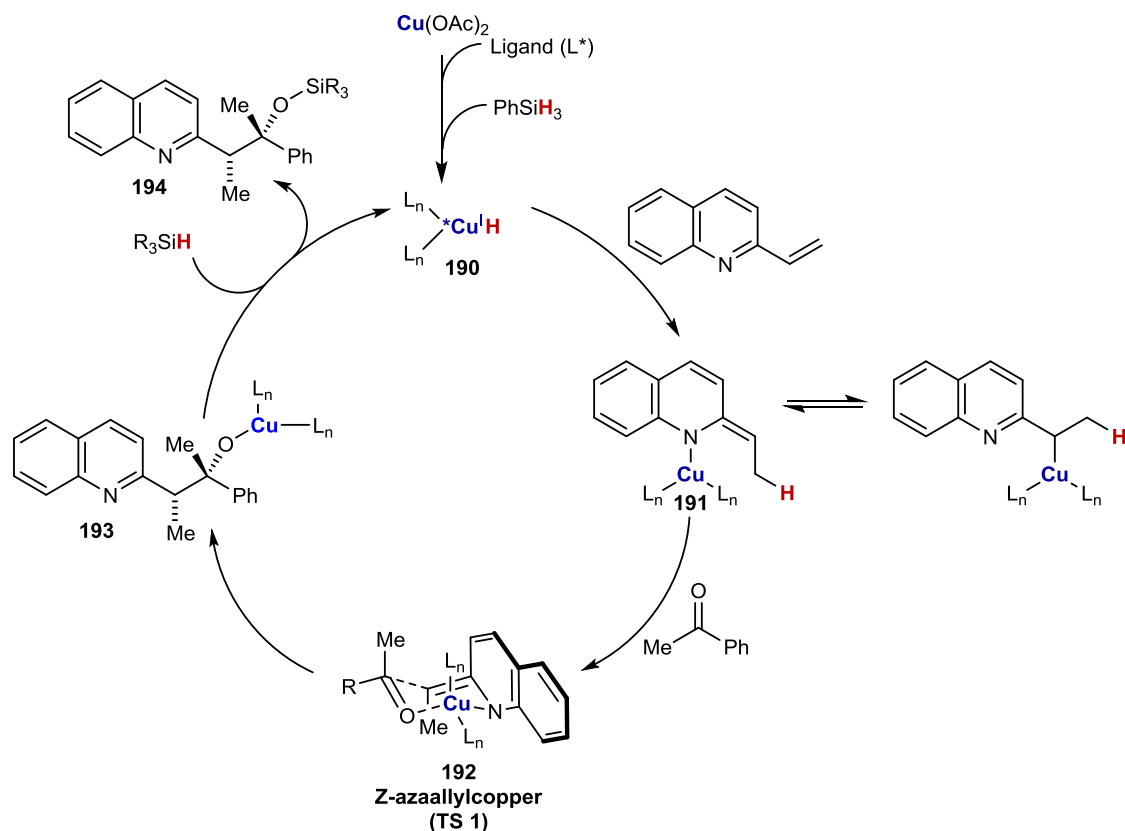
^a Reaction performed by Aakarsh Saxena

Scheme 2.12: Reductive Coupling of β -Substituted Alkenylazaarenes with Ketones

These reactions demonstrate alkenylazaarenes containing β -phenylethyl, methoxymethyl or ethyl groups smoothly underwent reductive coupling to deliver products **189a-189c** with good to high diastereoselectivities and excellent enantioselectivities. These products also encompassed additional examples of different azaarenes, such as a dimethoxytriazine (product **189a**), 1,3-pyrimidine (product **189b**) and diphenyloxazole (product **189c**).

In accordance with the accepted catalytic cycle of conjugate reduction of enoates,^{30d} a possible mechanism for the present copper-catalysed reductive coupling of alkenylazaarenes with ketones is described in Scheme 2.13 using 2-vinylquinoline (**175b**) for illustrative purposes. $\text{Cu}(\text{OAc})_2$ in the presence of bisphosphine **L4** and PhSiH_3 is reduced to generate ligated CuH species **190**, which undergoes a 1,4-reduction with 2-vinylquinoline (**175b**) to give complex **191**. Carbonyl addition

occurs via a six-membered transition state **192** to give copper alkoxide **193** which then undergoes σ -bond metathesis with PhSiH_3 to liberate the silylated product **194** (silyl deprotection occurs upon work-up to give product **186b**), regenerating the ligated CuH species **190** (Scheme 2.13).



Scheme 2.13: Postulated Catalytic System

Interestingly, the stereochemical outcome of the reaction exhibits a strong substrate dependence. For example, 2-vinylquinoline-containing products **186b-186c** were formed with the opposite sense of enantioinduction compared with 1-vinylisoquinoline-containing products **186d-186g** despite the same enantiomer of **L4** being employed throughout. In addition, different diastereochemical outcomes were obtained with cyclic as opposed to acyclic ketones. A six-membered Zimmerman-Traxler-type transition state is assumed to be adopted where the larger aryl group of the ketone occupies the pseudoequatorial position.⁷⁰ Figure 2.02 depicts conformations that are consistent with these observations.

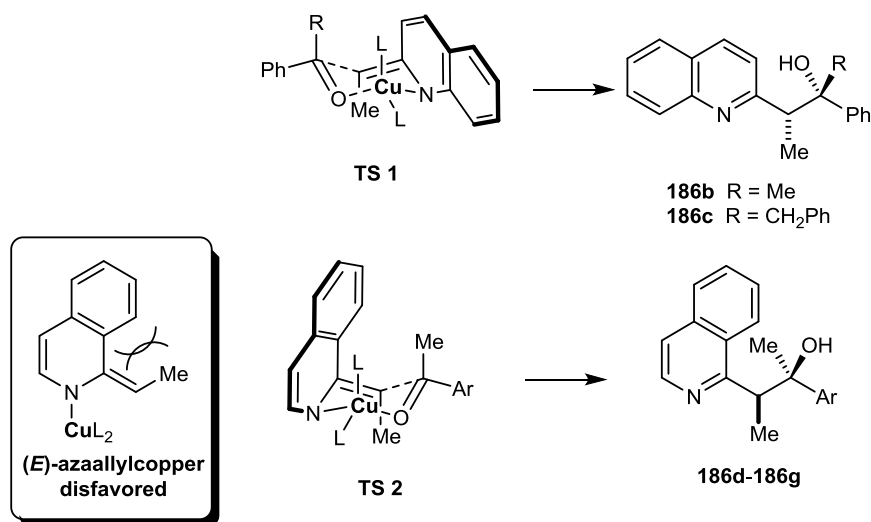


Figure 2.02: Rationalization of Stereochemical Outcomes **TS 1** and **TS 2**

TS 1 and **TS 2** depicts the conformations which are consistent with the participation of *Z*-azaallylcopper species for the reactions producing products **186b**, **186c** and **186d-186g**. The enantioinduction observed in **TS 1** is opposite to that in **TS 2** and the reasons for this are not clear at this present time. The preference for the *Z*-azaallylcopper species in **TS 2** can be explained by the severe A_{1,3}-strain⁷¹ that would disfavour the corresponding *E*-azaallylcopper species. However, a similar argument cannot be used to explain the same preference for **TS 1**. For reactions involving cyclic ketones (products **186h-186l**), reaction through the *E*-azaallylcopper species (or the *Z*-azaallyl copper species in the case of **186j**) appears to be favoured, as in **TS 3** for the formation of **186i** (Figure 2.07).

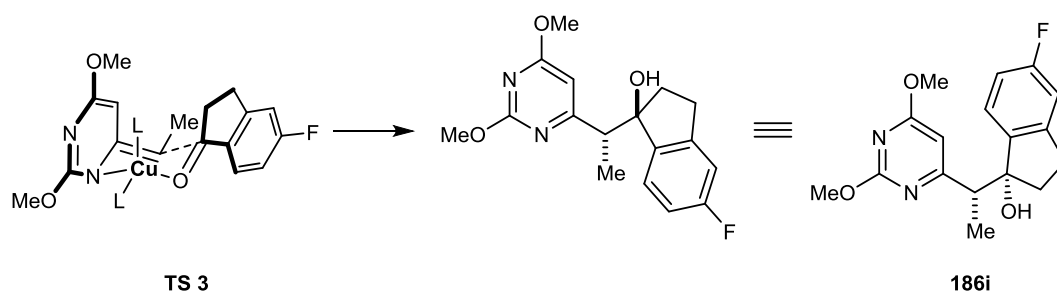
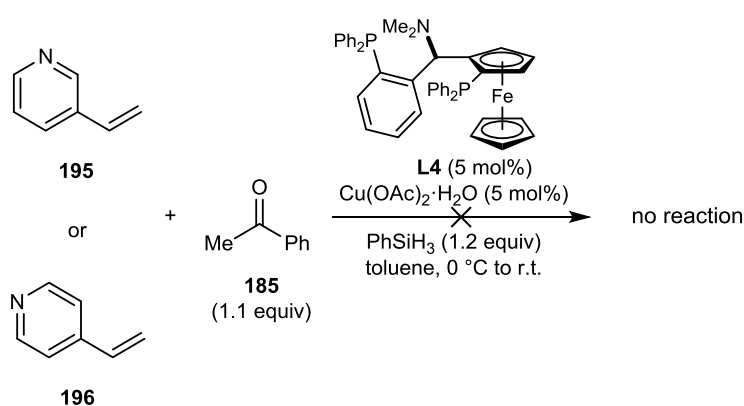


Figure 2.03: Rationalization of Stereochemical Outcomes **TS 3**

The discussion so far has been based upon the assumption that chair-like transition states are operative; however, reactions through boat-like structures cannot be

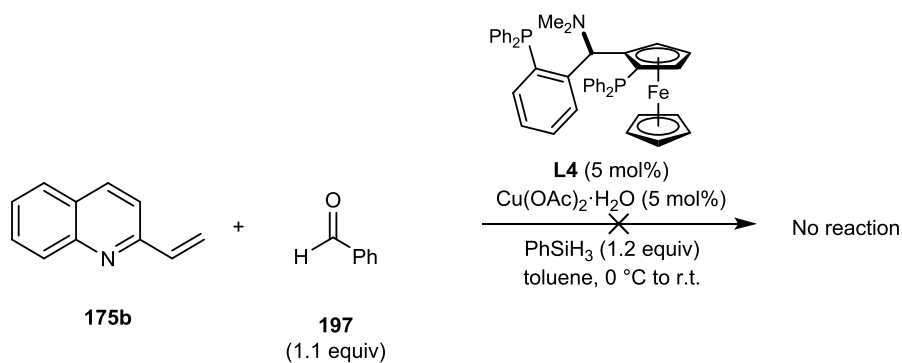
excluded. Further studies are required to investigate the interplay between sterics and/or electronic properties of the alkenylazaarene and ligand in order to determine the reasons for the observed stereochemical outcomes.

3-Vinylpyridine and 4-vinylpyridine (substrates **195** and **196**, respectively) did not participate in the reductive coupling reaction with acetophenone (**185**) (Scheme 2.14). From these observations, it suggests that coordination of the copper to the nitrogen atom on the azaarene is required in order to form the six-membered Zimmerman-Traxler-type transition state for the reaction to proceed. However, the possibility that these substrates are simply insufficiently activated under these reaction conditions cannot be excluded.



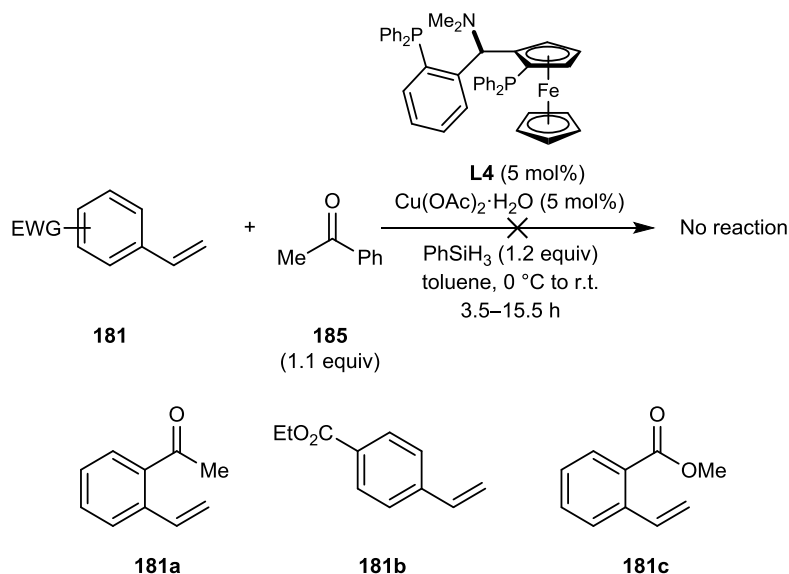
Scheme 2.14: Reductive Aldol Coupling of 3- and 4-Vinylpyridine

The use of aldehydes as electrophiles for this reaction was briefly explored. 2-Vinylquinoline **175b** and benzaldehyde (**197**) failed to undergo reductive coupling under the standard reaction conditions (Scheme 2.15). Analysis of the ^1H NMR spectrum of the crude reaction mixture showed peaks corresponding to unreacted **175b** and benzyl alcohol (product of reduction of benzaldehyde). As aldehydes are more reactive than ketones, it was postulated under our reaction conditions that the reduction of benzaldehyde to benzyl alcohol is preferential to the reduction of the olefin rendering the process ineffective for this particular reaction.



Scheme 2.15: Cu-Catalysed Reductive Coupling of 2-Vinylquinoline with Benzaldehyde

To test the scope of this process further, electron deficient vinylarenes were also synthesised as previously discussed. Attempts to couple electron deficient vinylarenes with acetophenone (**185**) were unsuccessful. These results indicate that the C=N moiety in azaarenes is crucial in activating the adjacent alkene and that combined with the ability to coordinate to the copper to form the six-membered transition state is necessary for the reaction to proceed under these reaction conditions (Scheme 2.16).



Scheme 2.16: Reductive Coupling of Electron Deficient Vinylarenes with Ketones

2.3 Application of Methodology

Ravuconazole⁷² and Voriconazole⁷³ are potent antifungal agents containing the key structural features embodied by the reductive coupling products in the methodology described in this chapter (Figure 2.04).

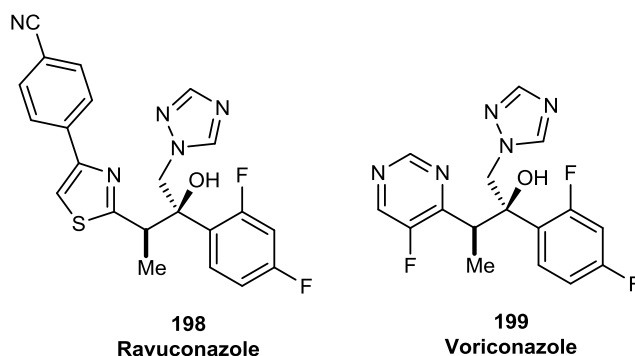
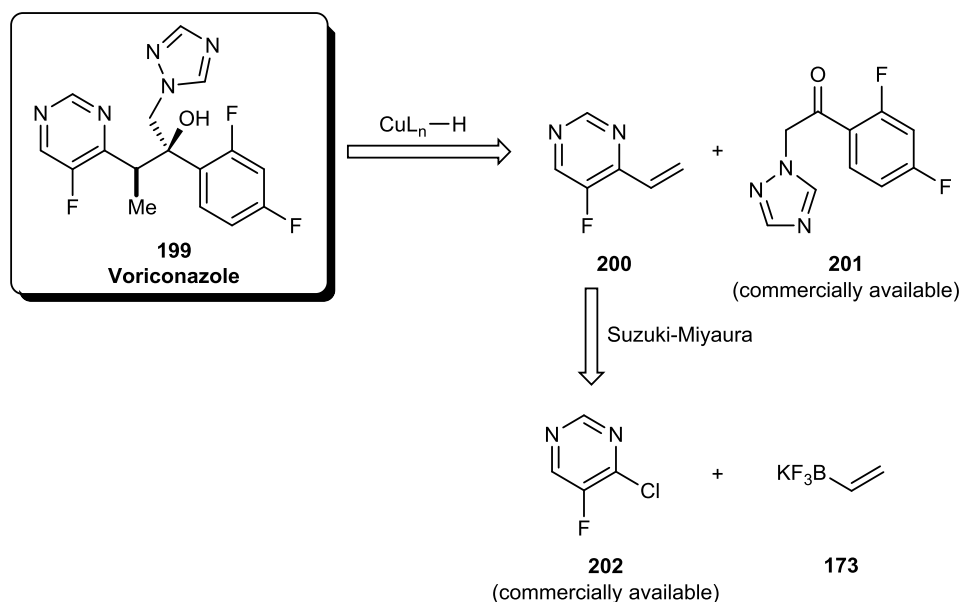


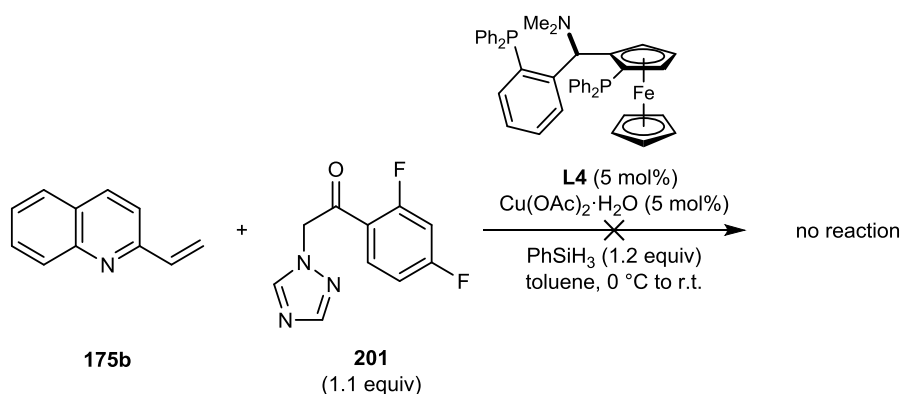
Figure 2.04: Structurally Relevant Pharmaceuticals

Voriconazole (**199**) was selected as an ideal target molecule for the copper-catalysed reductive coupling chemistry. Retrosynthetic analysis revealed a short two-step sequence towards the enantioselective synthesis of Voriconazole (Scheme 2.17).



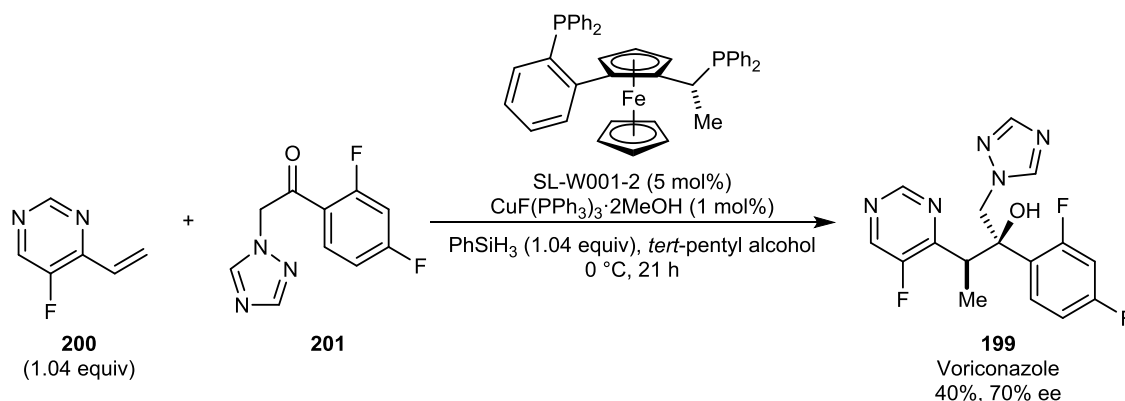
Scheme 2.17: Retrosynthetic Analysis of Voriconazole

As an initial test, the Cu-catalysed reductive coupling of 2-vinylquinoline **175b** with commercially available ketone **201** was attempted (Scheme 2.18). None of the coupled product was observed in the ^1H NMR spectrum of the crude reaction mixture. It is possible that the nitrogen atoms on the triazole ring of the ketone may be poisoning the system by strongly binding to the copper catalyst; however, the exact reasons are currently unclear. Further experimentation is needed to address this problem and to establish a short and enantioselective synthetic route to Voriconazole (**199**).



Scheme 2.18: Synthesis of Voriconazole Analogue

This was exemplified in a patent from Pfizer in 2014, relating to an improved process for the preparation of Voriconazole (**199**) citing our paper utilising the generation of copper nucleophiles from vinylazaarenes in an enantioselective addition to ketones (Scheme 2.19).⁷⁴



Scheme 2.19: Synthesis of Voriconazole

2.4 Conclusions

In summary, an enantioselective copper-catalysed reductive coupling of alkenylazaarenes with ketones has been developed.^{10c} The scope of the process is broad, and the enantioselectivities of the products were uniformly high. In addition to pyridine, other effective nitrogen containing heteroarenes included quinoline, isoquinoline, pyrimidines, quinoxaline and thiazole. A range of acyclic and cyclic ketones have also been shown to be effective coupling partners. The process is not limited to vinylazaarenes; β -substituted alkenylazaarenes are also effective coupling partners and the reactions proceed under mild conditions to deliver products in good to high levels of diastereo- and enantioselectivities. Functionality tolerated at the β -position of the alkene included ethyl, phenethyl and allylic ether group. This report has demonstrated the first examples of catalytic asymmetric reductive coupling of alkenylazaarenes with features that should be advantageous for application of this process in the preparation of novel enantioenriched chiral azaarene-containing building blocks.

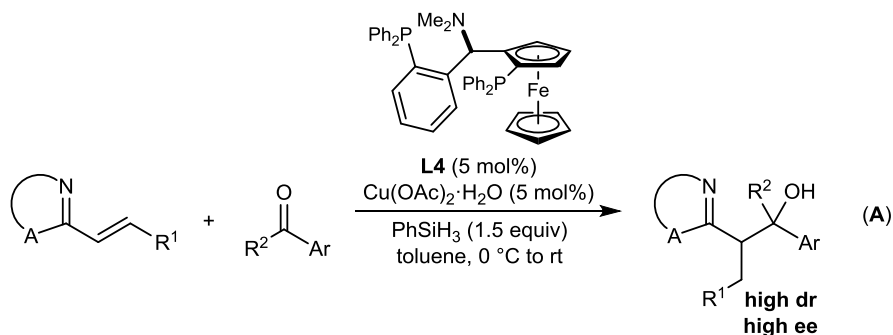
Essential structural requirements of the alkenylazaarenes were revealed when 3- and 4-vinylpyridine failed to undergo reductive coupling under the developed set of conditions. For the reaction to proceed the nitrogen atom must be at the 2-position within the azaarene so that it is in conjugation with the olefin and also so that it is in close proximity with the ligated-copper species to form the six-membered Zimmerman-Traxler-type transition state.

Finally, the synthesis of anti-fungal drug Voriconazole (**199**) was attempted. Despite our unsuccessful attempts, the synthesis was achieved through slight modification of our reaction conditions. We expect that the methodology developed should be applicable to the preparation of other novel enantioenriched chiral azaarene-containing building blocks.

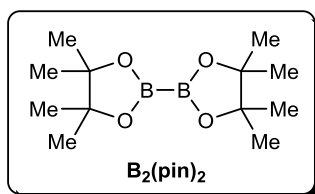
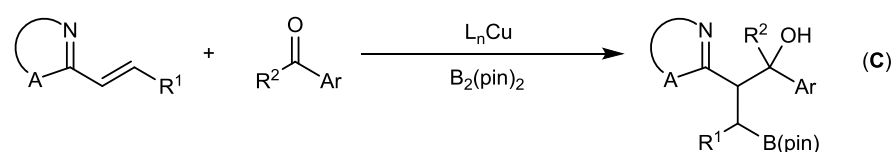
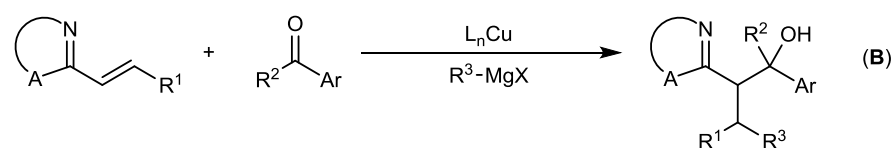
2.5 Future Work

The enantioselective copper-catalysed reductive coupling chemistry developed opens up two obvious avenues for future work in this area. It is anticipated that by changing from a hydride nucleophile to a carbon or heteroatom nucleophile this process would become more divergent, granting access to a variety of chiral compounds starting from a single substrate (Scheme 2.20). In this regard, the copper-catalysed 1,4-addition of Grignard reagents^{51b, 75} and boron reagents⁷⁶ is well preceded and development of such reactions to incorporate an azaarene moiety would be a valuable endeavour.

Initial C–H bond formation (this work):



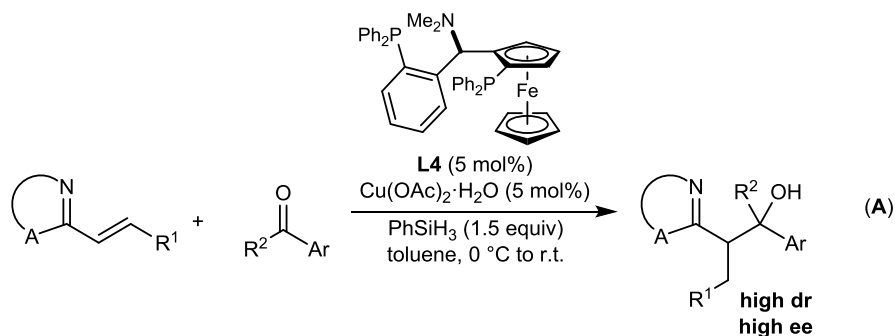
Initial C–C or C–B bond formation (future work):



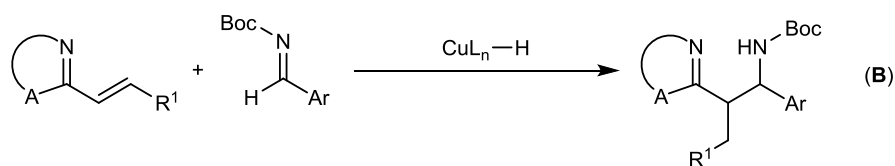
Scheme 2.20: Domino Conjugate Addition/ Aldol Coupling of Alkenylazaarenes

Alternatively, another avenue to explore is by changing the electrophile, resulting in the trapping of the organocopper intermediate by a different functional group (e.g. imines or allyl species) resulting in a diverse range of products (Scheme 2.21). In fact, trapping with imines to form β -amino heterocyclic species is the subject of the next chapter.

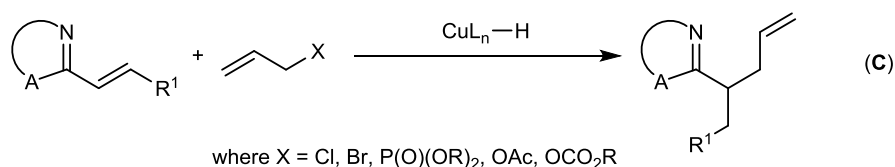
Trapping with ketone (this work):



Trapping with imine (future work):



Trapping with allylating agent (future work):



Scheme 2.21: Domino Conjugate Addition/Mannich Reaction or Conjugate Addition/Allylic Substitution Reaction of Alkenylazaarenes

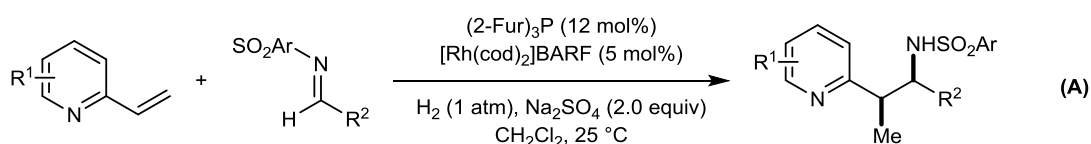
Finally, although attempts were made, it would be still be useful if the practicality of this methodology was displayed through its application towards synthesising a biologically active molecule. Such an application would demonstrate the utility of this methodology as an efficient tool for the generation of enantioenriched azaarene-containing motifs which, as discussed in chapter 1 are, commonly used building blocks in many facets of synthetic chemistry.

3. ENANTIOSELECTIVE REDUCTIVE COUPLINGS OF VINYLZAARENES WITH *N*-BOC ALDIMINES

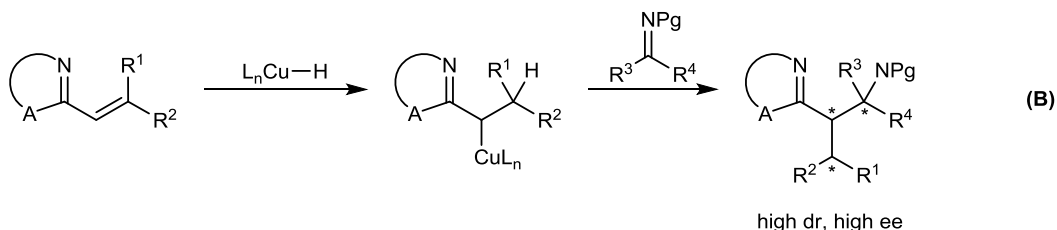
3.1 Aims and Objectives

Chapter 2 detailed the copper-catalysed reductive coupling of alkenylzaarenes with ketones; a process which enables the synthesis of azaarene-containing products with two contiguous stereocenters, including a tertiary alcohol.^{10c} The ability to employ other types of electrophiles would be beneficial to increasing the substrate scope and the utility of the reaction. As discussed in Chapter 1, Krische and co-workers described the racemic rhodium-catalysed hydrogenative coupling of vinylazines with *N*-sulfonylaldimines (Scheme 3.01A).⁶⁶ It was anticipated that a related enantioselective variant employing chiral copper hydride chemistry could be developed (Scheme 3.01B).

Krische's work:



Proposed work:



Scheme 3.01: Coupling of Vinylzaarenes with Imines

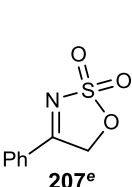
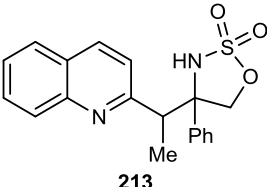
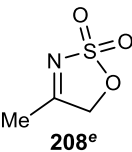
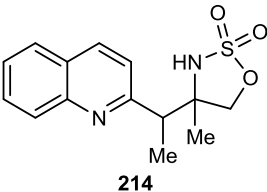
This would give rise to β -amino heterocycles with up to three stereocenters. It was hoped that control over both the relative and absolute stereochemistry could be achieved and subsequent deprotection of the protected amine could be realised to gain access to the free amine with no loss of enantiopurity.

3.2 Screening of Various *N*-Protected Imines

The project began with a screening of chiral bisphosphines in order to obtain the optimum ligand for this enantioselective copper-catalysed reductive coupling process. For the ligand evaluation, 2-vinylquinoline (**175b**) was selected as the azaarene substrate and a range of *N*-protected aldimines (**203-208**) was selected as coupling partner. Drawing on knowledge from a related study on copper-catalysed reductive couplings of alkenylazaarenes,^{10c} PhSiH₃ was selected as the hydride source, Cu(OAc)₂·H₂O as the source of copper and toluene as the solvent. Under these conditions, various chiral bisphosphine ligands were screened (Table 3.01).

Table 3.01: Cu-Catalysed Reductive Coupling of 2-Vinylquinoline with Aldimines

Entry	Imine	Product	Conversion (%) ^a	dr
1	 203 ^b	 209	57	3:1
2	 204 ^b	 210	40	4:1
3	 205 ^c	 211	>95	15:1
4	 206a	 212	>95	>19:1

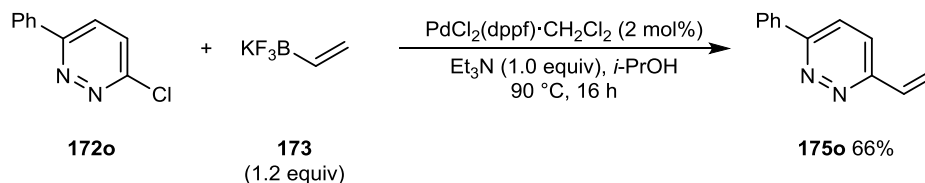
5	 207 ^e	 213	0	na
6 ^d	 208 ^e	 214	0	na

^aConversions were determined by ¹H NMR analysis of the unpurified reaction mixture, ^bSubstrate prepared by Dr Daniel Best, ^cSubstrate prepared by Joshua Smith, ^dReaction performed by Joshua Smith, ^eSubstrate prepared by Nawasit Chotsaeng

Pleasingly, the reductive coupled product was observed in all acyclic imines evaluated (entries 1-4). However, *N*-tosyl imine **203** and *N*-diphenylphoshinoyl imine **204** both gave poor conversions with significant quantities of starting material 2-vinylquinoline (**175b**) recovered (entries 1 and 2). With cyclic sulfamate imines (entries 5 and 6), only starting material was recovered. Promisingly, Cbz imine **205** and *N*-Boc imine **206a** both underwent the coupling efficiently with complete conversion to products. As the proof of concept had been established, the next step was to probe whether the reaction could proceed in a diastereo- and enantioselective manner. The reaction employing *N*-Boc imine **206a** (entry 4) was selected for further asymmetric development. Advantageously, *N*-Boc deprotection is normally facile. Employing imines that have an easily cleavable protecting group such as a Boc-group is synthetically beneficial as it should allow access to the free amine compounds and for sensitive functionality to be tolerated in the deprotection step.

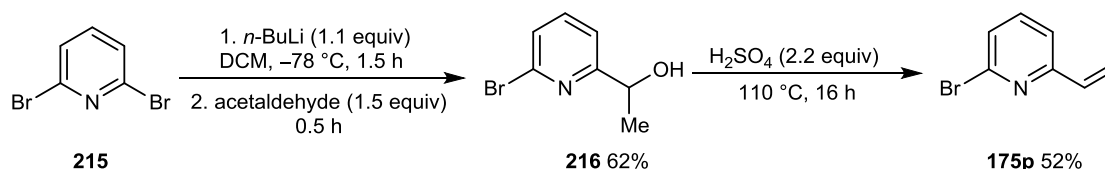
3.3 Preparation of Alkenylazaarenes

For the preparation of the azaarene coupling partner, the same synthetic strategy was utilised as seen in Chapter 2; preparation of 2-vinylazaarenes though Suzuki-Miyaura coupling between halogenated azaarenes **172** and potassium vinyltrifluoroborate (**173**). A range of 2-vinylazaarenes were synthesised using previously reported Suzuki-Miyaura cross-coupling conditions (Scheme 3.05 and see Scheme 2.03).⁶⁷



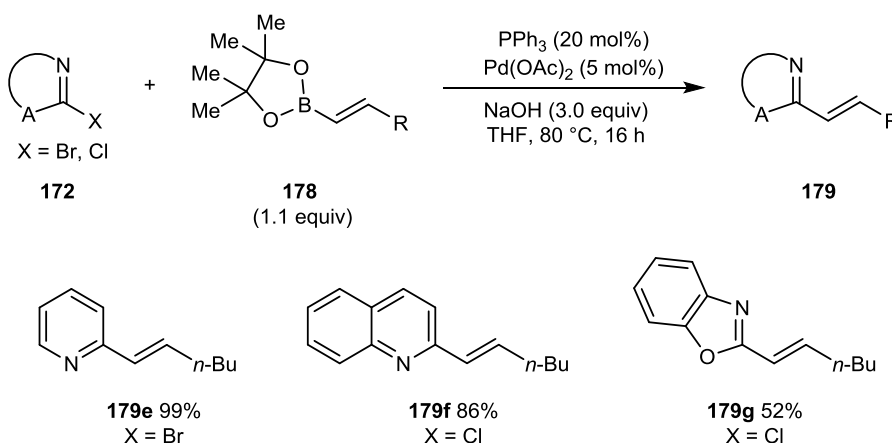
Scheme 3.05: Preparation of 2-Vinylazaarene **175o**

An alternative two step synthetic route was employed for the synthesis of 2-bromo-6-vinylpyridine (**175p**) (Scheme 3.06).⁶⁶ Treatment of 2,6-dibromopyridine (**215**) with *n*-BuLi provided the 2-lithiated pyridine species, which, in the presence of acetaldehyde, forms alcohol **216**. Dehydration of alcohol **216** by H₂SO₄ provides 2-bromo-6-vinylpyridine (**175p**) in moderate yield.



Scheme 3.06: Synthesis of 2-Bromo-6-Vinylpyridine

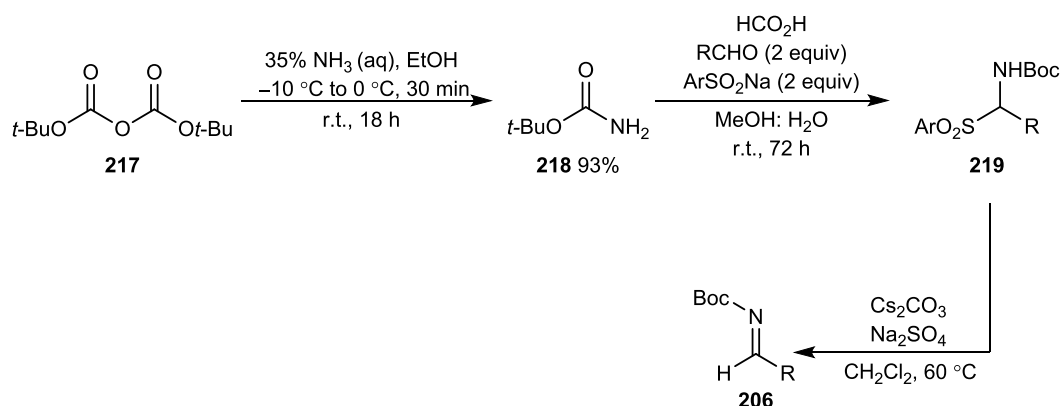
β -Substituted 2-alkenylazaarenes were prepared by coupling alkenylboronic acid pinacol esters, prepared from the previous study (Chapter 2), with halogenated azaarenes **172** using standard Suzuki-Miyaura cross-coupling procedures (Scheme 3.07). The reactions proceeded efficiently and β -substituted alkenylazaarenes **179e**-**179g** were isolated in good yields.



Scheme 3.07: Synthesis of β -Substituted 2-Alkenylazaarenes

3.4 Preparation of *N*-Boc Aldimines

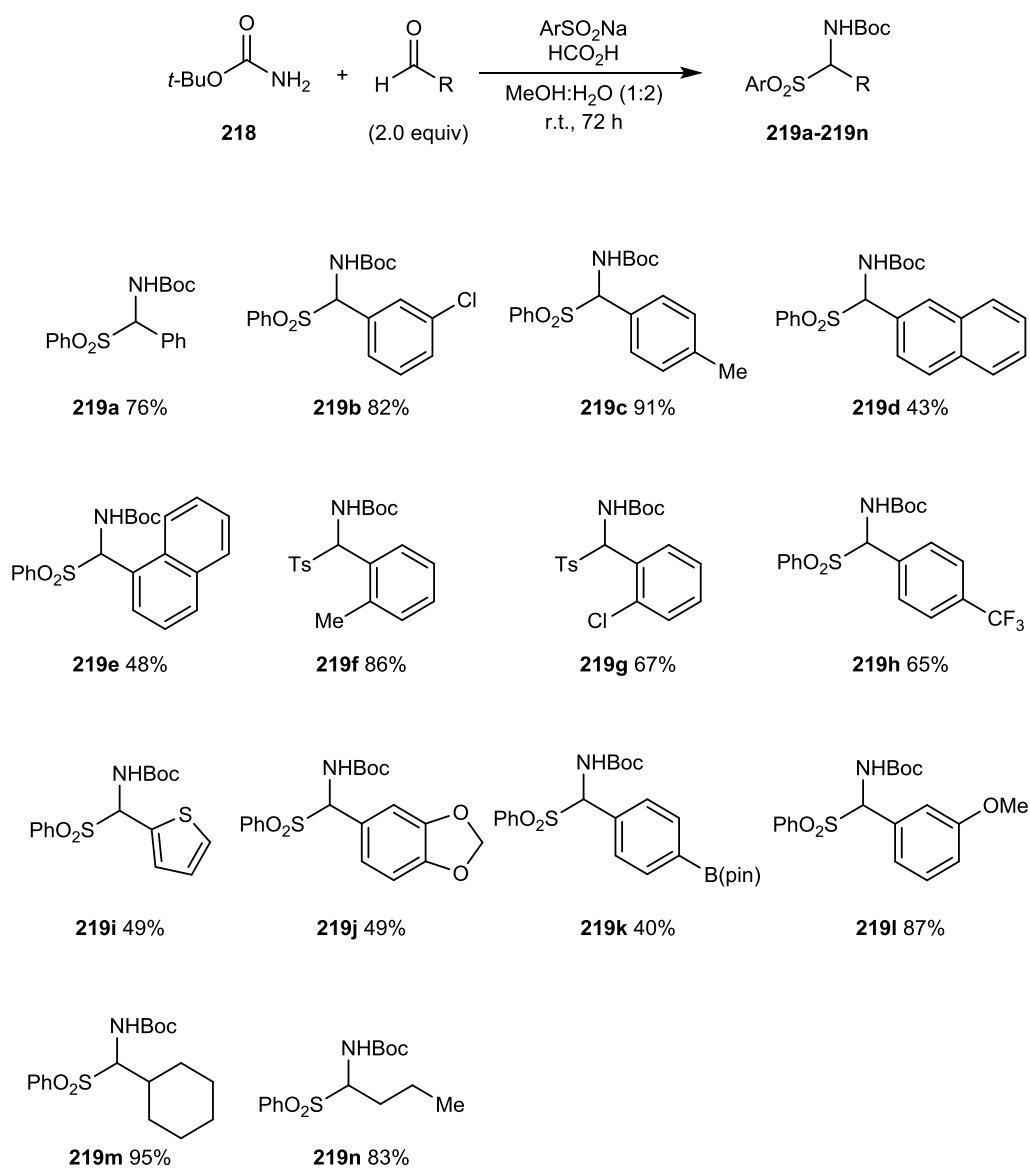
Various *N*-Boc aldimines were synthesised following the general procedure as illustrated in Scheme 3.02.



Scheme 3.02: Strategy for the Synthesis of *N*-Boc Aldimines

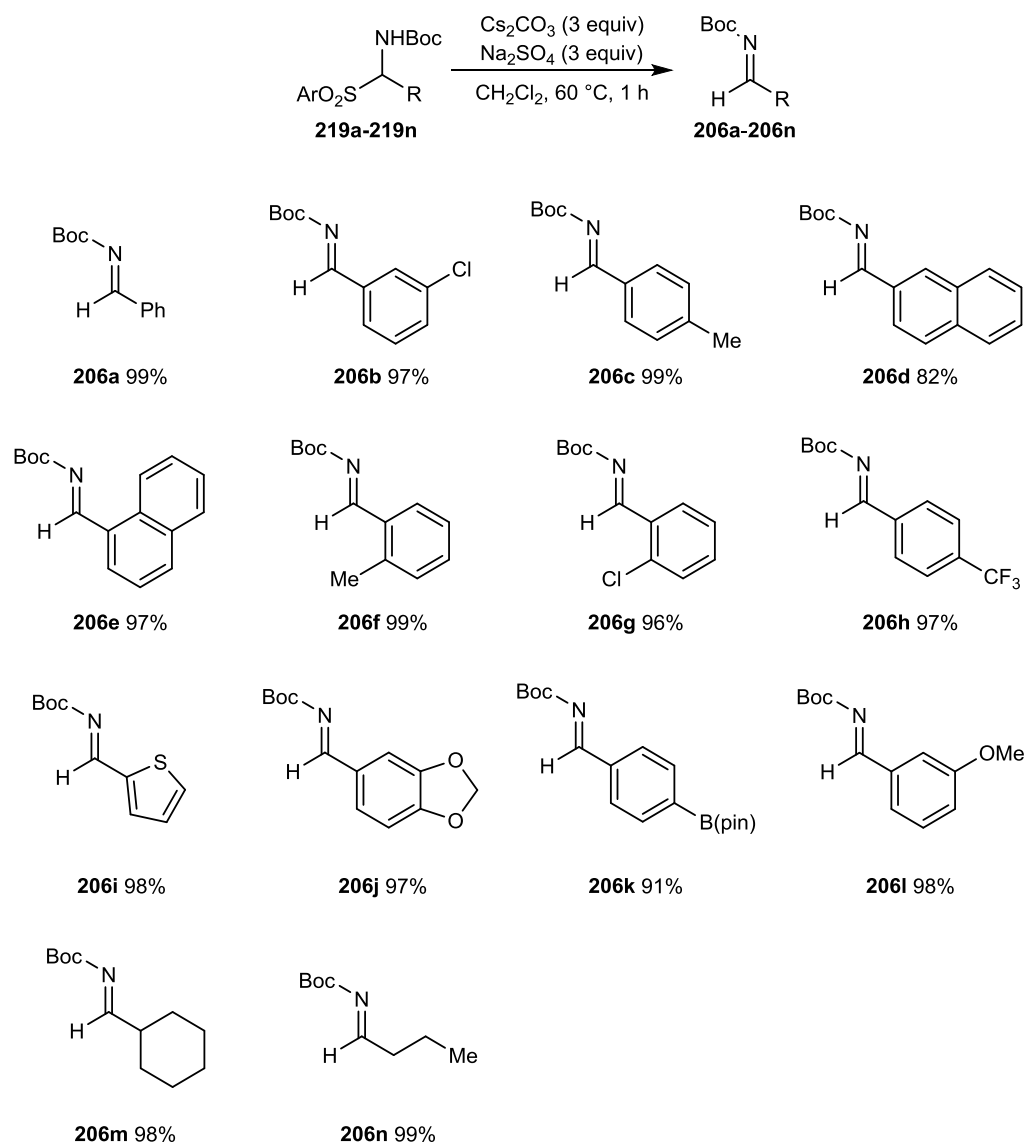
Despite being commercially available, *tert*-butyl carbamate (**218**) was conveniently prepared in a one-step procedure from Boc-anhydride (**217**). *tert*-Butyl carbamate (**218**) was isolated in excellent yields after recrystallisation (Scheme 3.02).

Next, the required sulfonylcarbamates **219**, a synthetic precursor of *N*-Boc aldimines were readily prepared following a modified literature procedure⁷⁷ using *tert*-butyl carbamate (**218**), various commercially available aromatic and aliphatic aldehydes and sodium benzenesulfinate or sodium 4-methylbenzenesulfinate suspended in a solution of $\text{H}_2\text{O}/\text{MeOH}/\text{formic acid}$ (Scheme 3.03).



Scheme 3.03: Synthesis of Sulfonylcarbamates

With the sulfonylcarbamates in hand, the corresponding *N*-Boc aldimines (**206a-206n**) were synthesised in excellent yields through the elimination of ArSO₂H under basic conditions (Scheme 3.04).



Scheme 3.04: Synthesis of *N*-Boc Aldimines

3.5 Ligand Screen and Optimisations

With both sets of substrates in hand, investigations began into the enantioselective CuH-catalysed reductive coupling of 2-alkenylazaarenes with *N*-Boc aldimines. First, an evaluation of various chiral bisphosphines was performed in order to determine the optimum ligand for this process. For ligand evaluation, 2-vinylquinoline (**175b**) was selected as the azaarene substrate and phenyl *N*-boc imine (**206a**) was selected as imine coupling partner. The initial ligand screen was performed under similar reaction conditions to those used in the previous study of enantioselective copper-catalysed reductive coupling of alkenylazaarenes with ketones (Table 3.02).^{10c}

Table 3.02: Evaluation of Chiral Bisphosphines for the Cu-Catalysed Reductive Coupling of 2-Vinylquinoline with *N*-Boc Imine^a

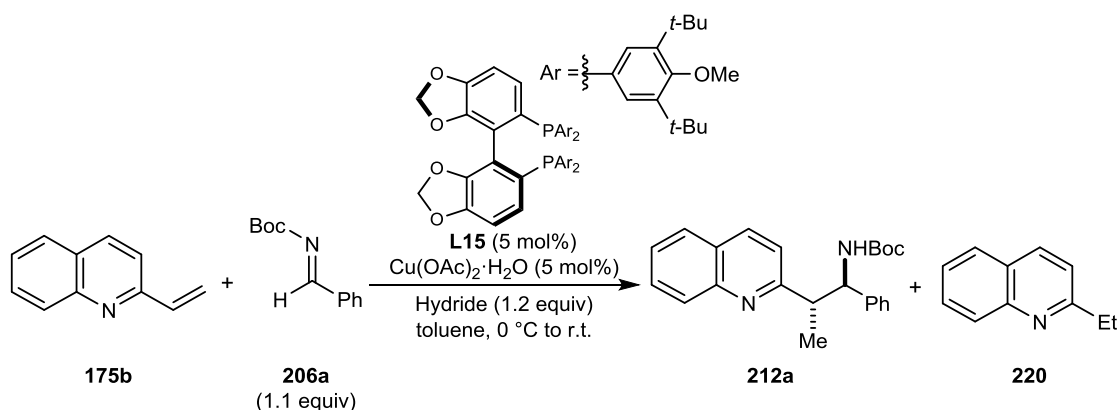
175b	206a (1.1 equiv)		212a	220
(<i>S</i>)-PhanePhos (L7)	Taniaphos SL-T001-1 (L8)		Josiphos SL-J002-1 (L9)	
(<i>R</i>)-BINAP (L10)	(<i>R</i>)-MeO-BIPHEP (L11)		(<i>R,R</i>)-QuinoxP* (L12)	
(<i>R,R</i>)-Ph-BPE (L13)	Josiphos SL-J006-1 (L14)		(<i>S</i>)-DTBM-SEGPHOS (L15)	
Entry	Ligand	212a:220^b	dr ^b	ee (%) ^c
1	L7	9:1	5:1	51
2	L8	19:1	6:1	56
3	L9	5:1	13:1	33
4	L10	6:1	19:1	25
5	L11	13:1	19:1	45
6	L12	19:1	19:1	1
7	L13	19:1	19:1	79
8	L14	18:1	19:1	69
9	L15	19:1	19:1	82

^aReactions were conducted using 0.1 mmol of **175b**. ^bDetermined by ¹H NMR analysis of the unpurified reaction mixtures. ^cDetermined by chiral HPLC analysis.

Pleasingly, most ligands evaluated showed promising chemoselectivity (in terms of the ratio of product to reduced starting material), diastereo- and enantioselectivity. With (*S*)-PhanePhos (**L7**), a Taniaphos ligand (**L8**) and a Josiphos ligand (**L9**) both enantioselectivity and diastereoselectivity were moderate. High diastereoselectivities were obtained with **L10-L15** (entries 4 to 9); however, only good enantioselection were observed with (*R,R*)-Ph-BPE (**L13**), the Josiphos ligand (**L14**) and (*S*)-DTBM-Segphos (**L15**). (*S*)-DTBM-Segphos (**L15**) was identified as the most effective chiral ligand for this reaction as it also displayed high chemoselectivity (ratio of **212a**:**220**) combined with high enantio- and diastereoselectivities.

Reaction optimisation studies were conducted by my co-worker Aakarsh Saxena. With regards to the hydride source, all those evaluated gave excellent diastereoselectivities (Table 3.03). Modest enantioselectivities were observed using poly(methylhydrosiloxane) (PMHS) and Ph_2SiH_2 . PhSiH_3 and pinacolborane both provided products with good enantioselectivities; however enantioselectivity was superior when employing 1,1,3,3-tetramethyldisiloxane (TMDS). The use of $(\text{EtO})_3\text{SiH}$ as hydride showed significant quantities of the 2-vinylquinoline in the ^1H NMR spectrum of the unpurified reaction mixture and no identifiable peaks corresponding to the coupled product were observed.

Table 3.03: Evaluation of Source of Hydride^a

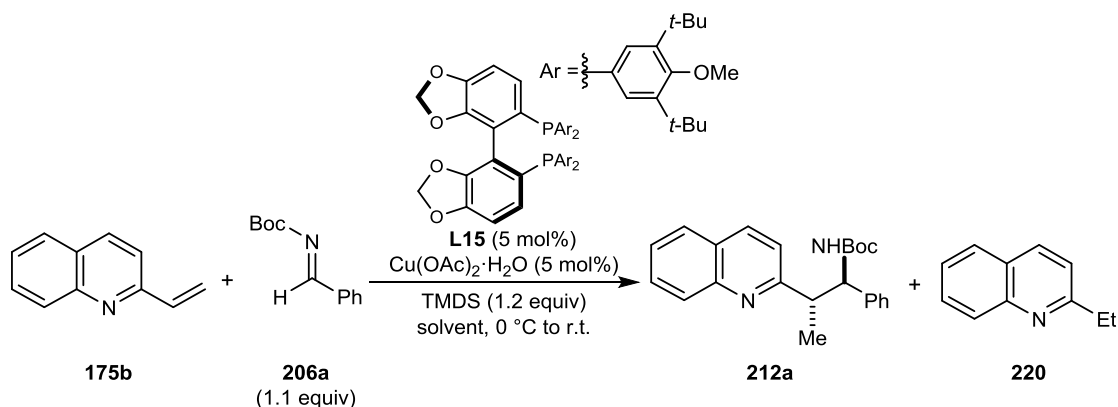


Entry ^b	Hydride	dr ^c	ee (%) ^d
1	PhSiH ₃	19:1	81
2	TMDS	19:1	87
3	PMHS	19:1	75
4	(EtO) ₃ SiH	--	--
5	Ph ₂ SiH ₂	19:1	68
6	(pin)BH	19:1	81

^aReactions were conducted using 0.1 mmol of **175b**. ^bReaction performed by Aakarsh Saxena. ^cDetermined by ¹H NMR analysis of the unpurified reaction mixtures. ^dDetermined by chiral HPLC analysis.

With respect to the solvent; THF, Et₂O, toluene and 1,4-dioxane all afforded product **212a** with high diastereoselectivities and good enantioselectivities (Table 3.04). However, THF was the only solvent which gave complete dissolution of all the reagents at the start of the reaction; therefore, THF was chosen as the preferred solvent for this process.

Table 3.04: Evaluation of Solvent^a

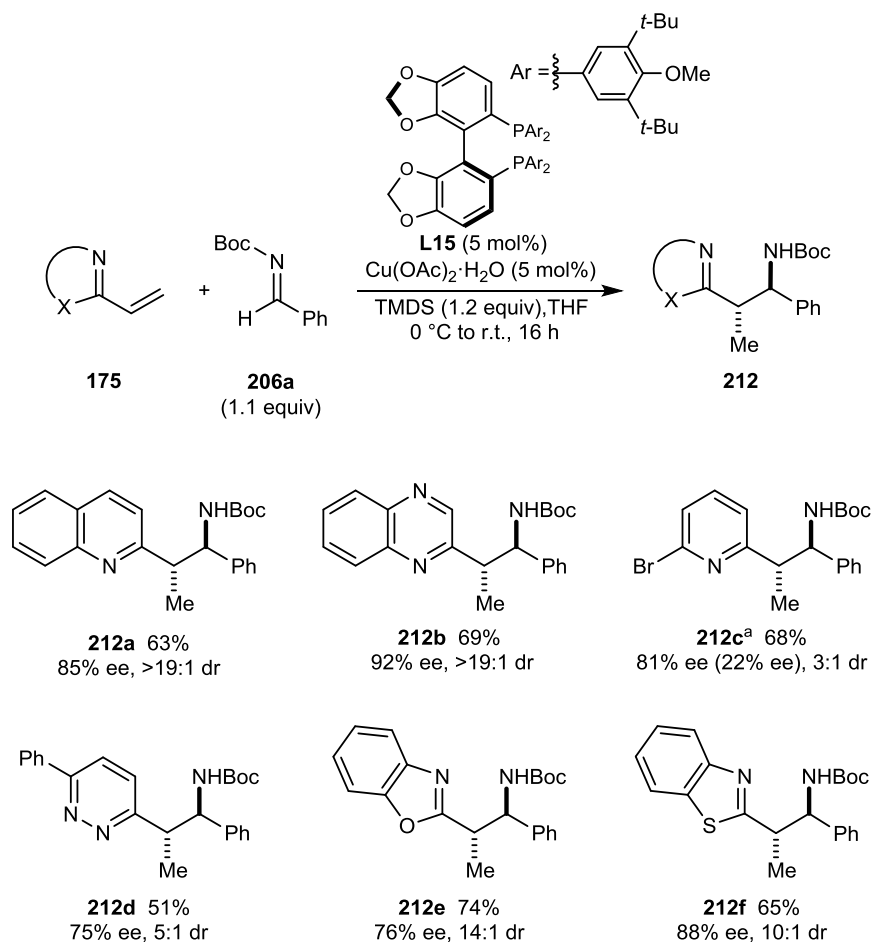


Entry ^b	Solvent	dr ^c	ee (%) ^d
1	Et ₂ O	19:1	76
2	THF	19:1	85
3	toluene	19:1	87
4	CH ₂ Cl ₂	--	--
5	1,4-dioxane	19:1	88

^aReactions were conducted using 0.1 mmol of **175b**. ^bReaction performed by Aakarsh Saxena. ^cDetermined by ¹H NMR analysis of the unpurified reaction mixtures. ^dDetermined by chiral HPLC analysis.

3.5.1 Substrate Scope

Application of the optimised conditions to the reaction of various 2-vinylazaarenes with phenyl *N*-Boc-protected imine **206a** gave the reductive coupled products in good yields and good to high enantio- and diastereoselectivities (Scheme 3.08).



Unless stated otherwise, yields are of pure isolated major diastereomers

^aIsolated as a mixture of diastereomers. The enantiomeric excess of the minor diastereomer is indicated in the parentheses.

Scheme 3.08: Reductive Coupling of Vinylazaarenes with *N*-Boc imine **206a**

In the presence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (5 mol%), **L15** (5 mol%) and TMDS (1.2 equiv), the reaction proceeded smoothly in THF at room temperature to give the reductive coupling product **212a** as the *anti*-diastereomer in 63% yield, excellent diastereoselectivity (>19:1 dr) and good enantioselectivity (85% ee). Other effective azaarenes included quinoxaline (**212b**), a bromopyridine (**212c**), a phenylpyridazine

(**212d**), benzoxazole (**212e**) and benzothiazole (**212f**). Vinylazaarenes containing benzannulation gave products with notably higher diastereoselectivities (products **212a**, **212b**, **212e** and **212f**), while 6-bromopyridine and 3-phenyl-6-vinylpyridazine resulted in more modest diastereoselectivities (**212c** and **212d**). In the case of 6-bromo-2-vinylpyridine the diastereomers were difficult to separate completely and the minor isomer was formed in a much lower enantiomeric excess (20% ee) compared with the major isomer (80% ee).

The relative and absolute stereochemistry of benzothiazole-containing product **212f** was determined by single crystal X-ray crystallography using a copper radiation source (Figure 3.01). The absolute and relative configurations of **212a-212e** were assigned by analogy with that observed in **212f**.

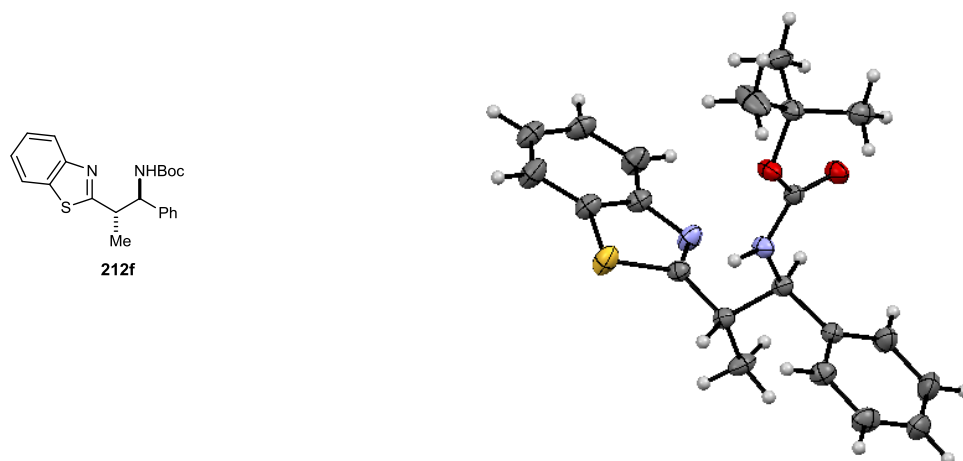
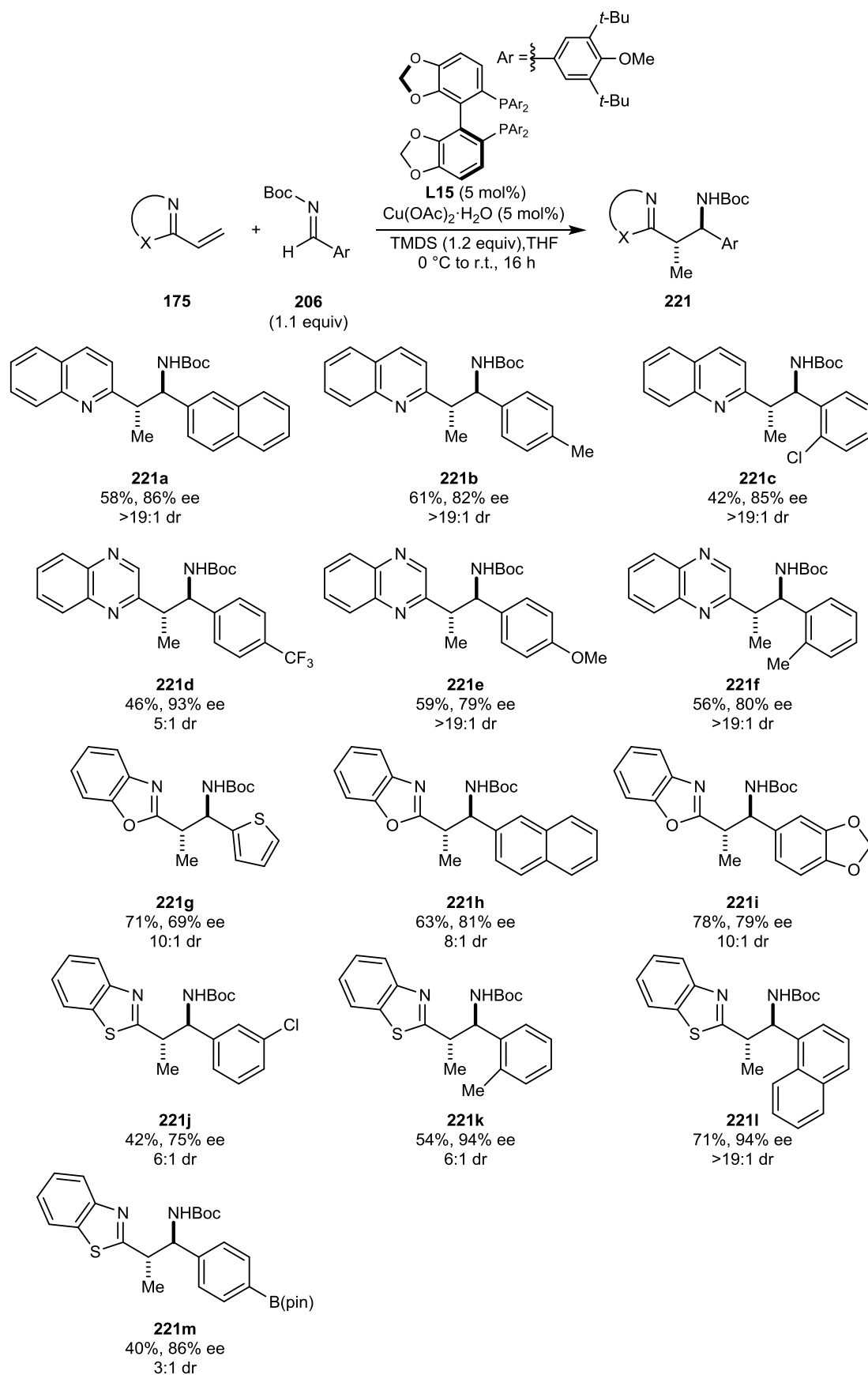


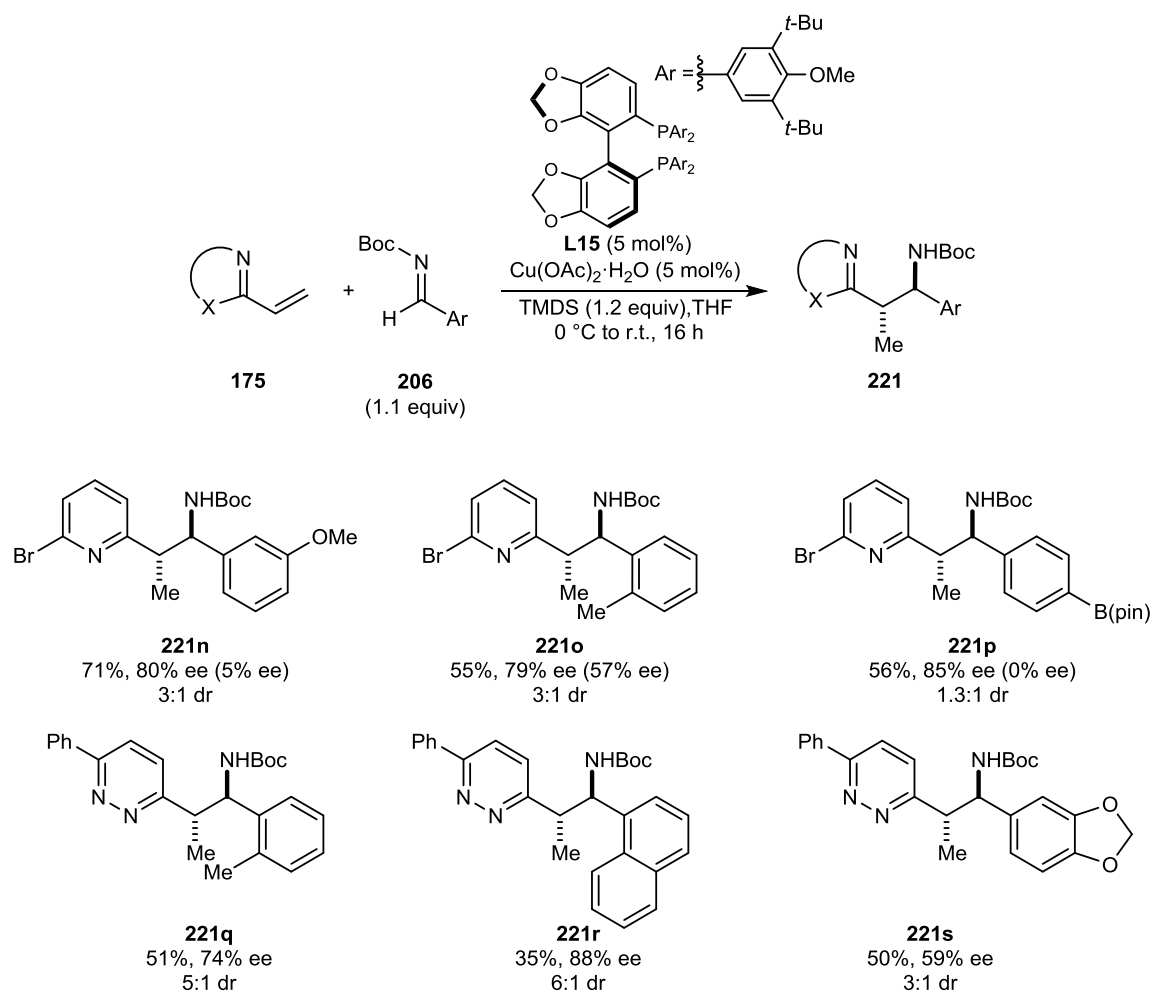
Figure 3.01: Stereochemical Determination of **212f**

Subsequently, the focus shifted to broadening the scope of the reaction to include various (hetero)aromatic *N*-Boc aldimines **206b-206l** (Scheme 3.09 and Scheme 3.10). Aromatic imines with substituents at the *ortho*-, *meta*- and *para*-positions on the phenyl ring (such as methyl, chloro, trifluoromethyl or methoxy) underwent the addition reaction successfully with a range of different 2-vinylazaarenes in modest yields and moderate to high enantio- and diastereoselectivities. Furthermore, reactions of imines containing 1-naphthyl, 2-naphthyl, 2-thienyl, dioxolane or boronate esters were also successful. For 2-vinylquinoline-containing products (**221a-221c**), all imines evaluated gave modest yields, high diastereoselectivities and good enantioselectivities. Quinoxaline-containing products (**221d-221e**) demonstrated the reaction tolerated *N*-Boc imines with electron-withdrawing groups (**221d**) and electron-donating groups (**221e**) on the aryl ring. However, a noticeable decrease in diastereoselectivity was observed when an imine encompassing an electron-withdrawing group is employed (*e.g.* adduct **221d** *vs.* **221e** and **221f**). Diastereoselectivities were generally lower for benzoxazole-containing products (**221g-221i**) compared with quinoline-containing and quinoxaline-containing products. Excellent enantioselectivities were observed for benzothiazoles-containing products when coupled with a *para*- substituent on the imine (product **221k**) or 1-naphthyl-containing imine (product **221l**).



Scheme 3.09: Reductive Coupling of Benzannulated Vinylazaarenes **175** with Various *N*-Boc Imines

As observed previously (Scheme 3.08), the reactions of non-benzannulated azaarenes; 2-bromo-6-vinylpyridine and 3-phenyl-6-vinylpyridazine generally gave lower diastereoselectivities (products **221n-221s**) as shown in Scheme 3.10. Lower diastereoselectivities were also obtained with an imine containing a *p*-pinacol boronic ester (**221m** and **221p**). Interestingly, the minor diastereomers obtained for products **221n** and **221p** were obtained in low or non-existent enantiomeric excesses.



Scheme 3.10: Reductive Coupling of Vinyl-Pyridines and Pyridazines **175** with Various *N*-Boc Imines

Compared with the results shown in Scheme 3.07 and with similar reactions using ketones as electrophiles,^{10c} these reactions often provided lower yields of the reductive coupling products due to more prevalent side reactions, such as reduction of both reaction partners without C-C bond formation. Although no definitive trends could be deduced from the particular combinations of substrates that resulted in the

highest enantioselectivities, values of 85% enantiomeric excess or higher were observed in several cases (**221a**, **221c**, **221d**, **221k-221m**, **221p** **221r**).

The relative and absolute stereochemistry of quinoxaline-containing product **221d** and pyridazine-containing product **221r** was determined by single crystal X-ray crystallography using a copper radiation source (Figure 3.02). The relative and absolute configurations of **221a-221c**, **221e-221p** and **221s** were assigned by analogy to that observed in **221d** and **221r** which was also consistent with the observed sense of enantioinduction in product **221f**.

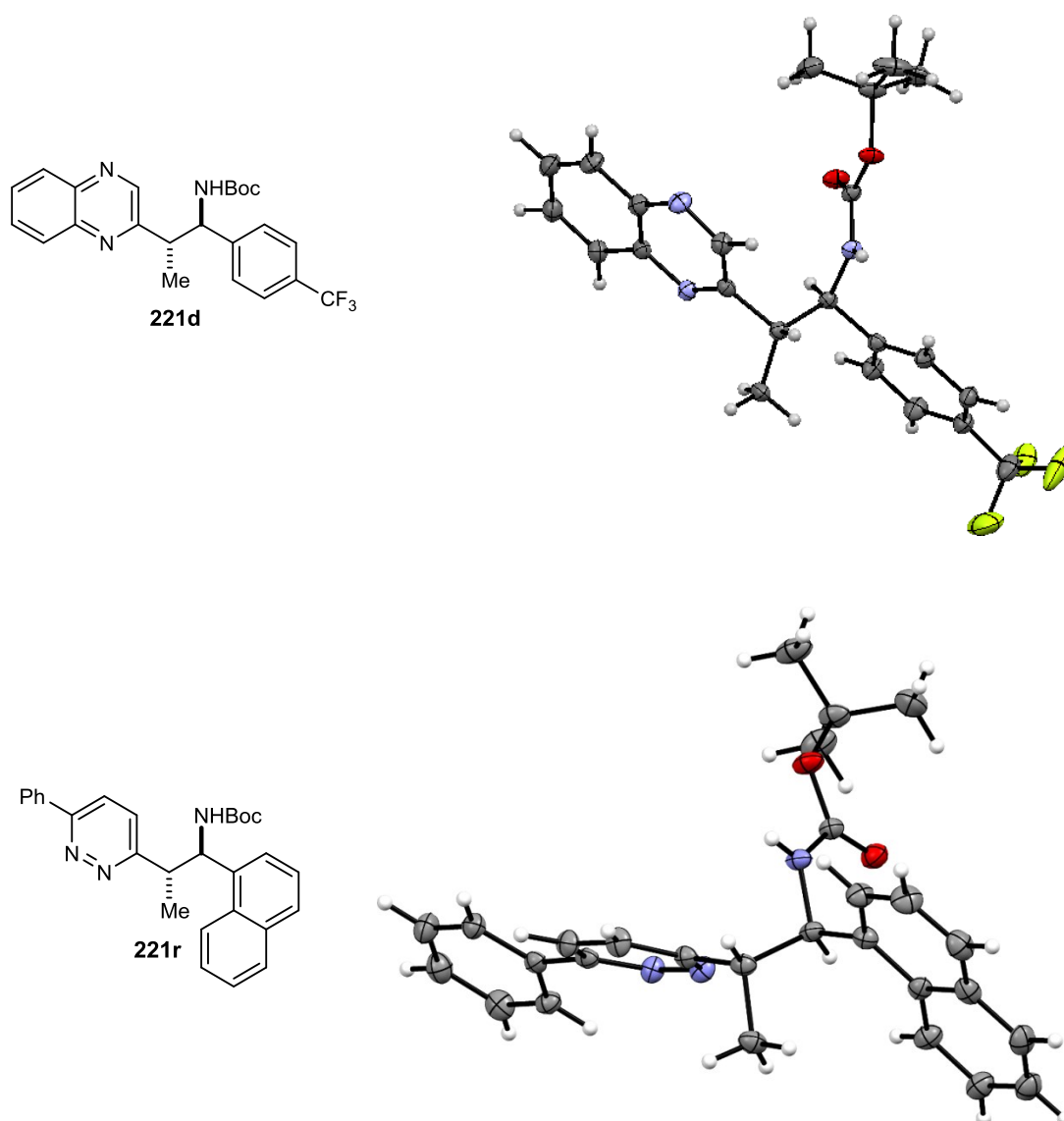
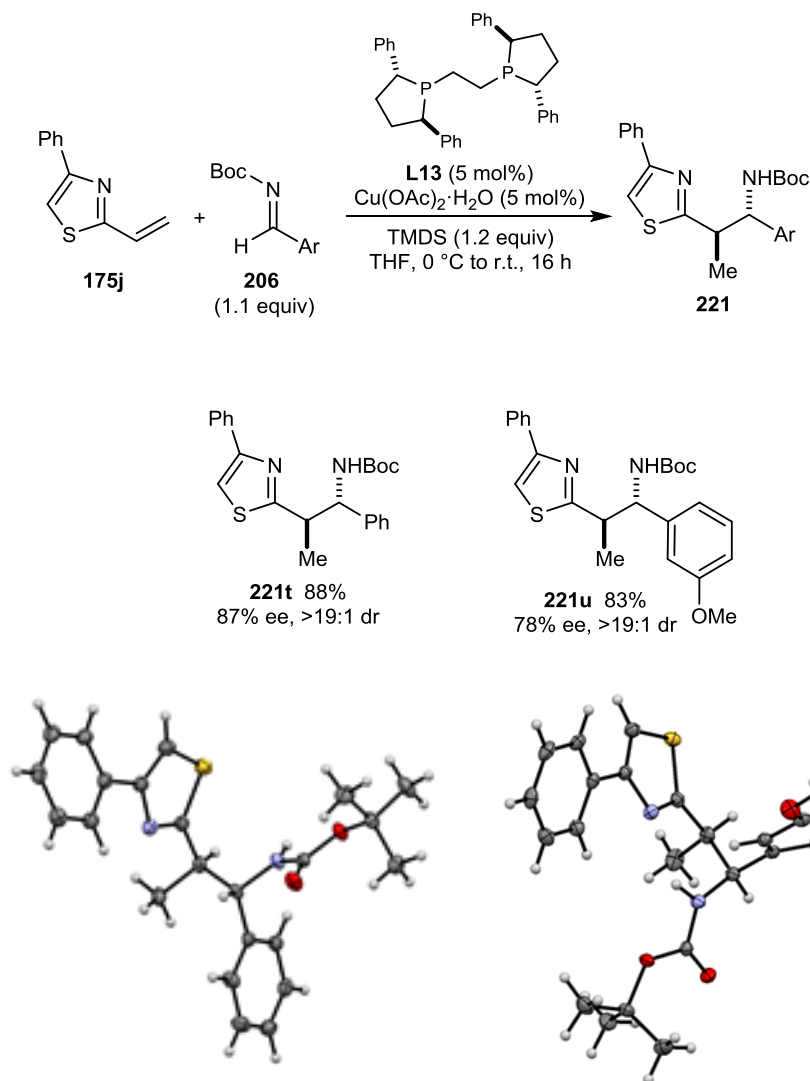


Figure 3.02: Stereochemical Determination of **221d** and **221r**

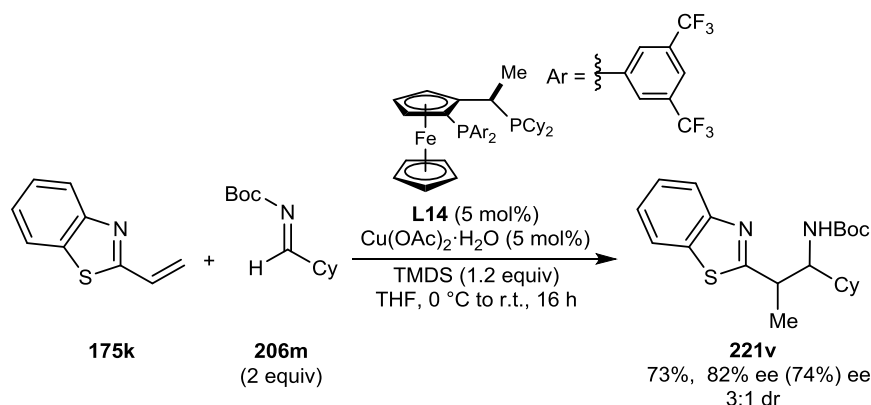
The reductive coupling of 4-phenyl-2-vinylthiazole (**175j**) with imines **206a** and **206l** proceeded with low enantioselectivity using ligand **L15**. Fortunately, (*R,R*)-Ph-BPE (**L13**) provided improved results and gave **221t** in 88% yield, >19:1 dr, and 87% ee and **221u** with 83% yield, >19:1 dr and 78% ee (Scheme 3.11).



Scheme 3.11: Reductive coupling of **175j** with Various *N*-Boc Imines using **L13**

Again, X-ray crystallography confirmed the relative and absolute stereochemistry of products **221t** and **221u**.

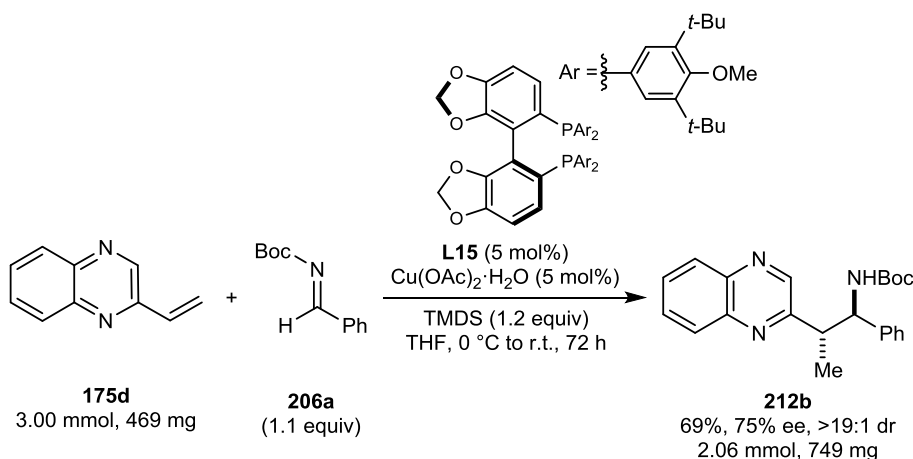
The reaction of 2-vinylbenzothiazole (**175k**) with an imine **206m** (2.0 equiv) containing an aliphatic substituent (cyclohexyl) was also studied (Scheme 3.12). Although low enantioselectivities were obtained using ligands **L13** or **L15**, the Josiphos ligand SL-J006-1 (**L14**) gave improved results and provided the two diastereomers of **221v** in 73% and 16% yields, in 82% and 74% enantiomeric excess for the major and minor isomers, respectively.



Scheme 3.12: Reductive coupling of **175k** with **206m** using **L12**

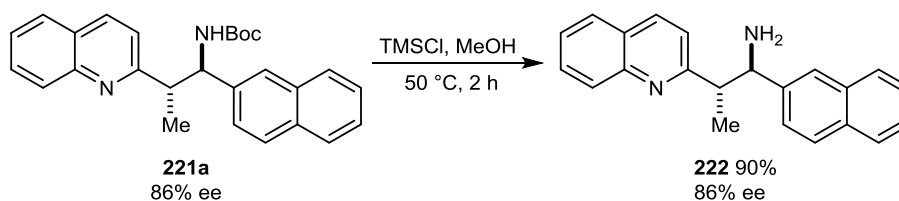
3.5.2 Larger Scale Reaction and Deprotection

It is also possible to conduct this process on a larger scale. For example, reductive coupling of 2-vinylquinoxaline (**175d**) on a 3.00 mmol scale using *N*-Boc imine **206a** (1.1 equiv) in the presence of $\text{CuO}(\text{Ac})_2\cdot\text{H}_2\text{O}$ (5 mol%), (*S*)-DTBM-SEGPHOS (5 mol%) and TMDS (1.2 equiv) provided **212b** in 69% yield (750 mg) and 75% ee (Scheme 3.13) (*cf* 69% yield and 92% *ee* on a 0.3 mmol scale see Scheme 3.07). The significant drop in enantioselectivity could be attributed to the uneven cooling of the reaction vessel. Rapid addition of the organosilane may have also resulted in an exotherm thereby raising the temperature of the reaction mixture, which could result in a loss of enantiocontrol.



Scheme 3.13: Larger Scale Enantioselective Cu-Catalysed Reductive Coupling of **175d** with Phenyl *N*-Boc Imine **206a**

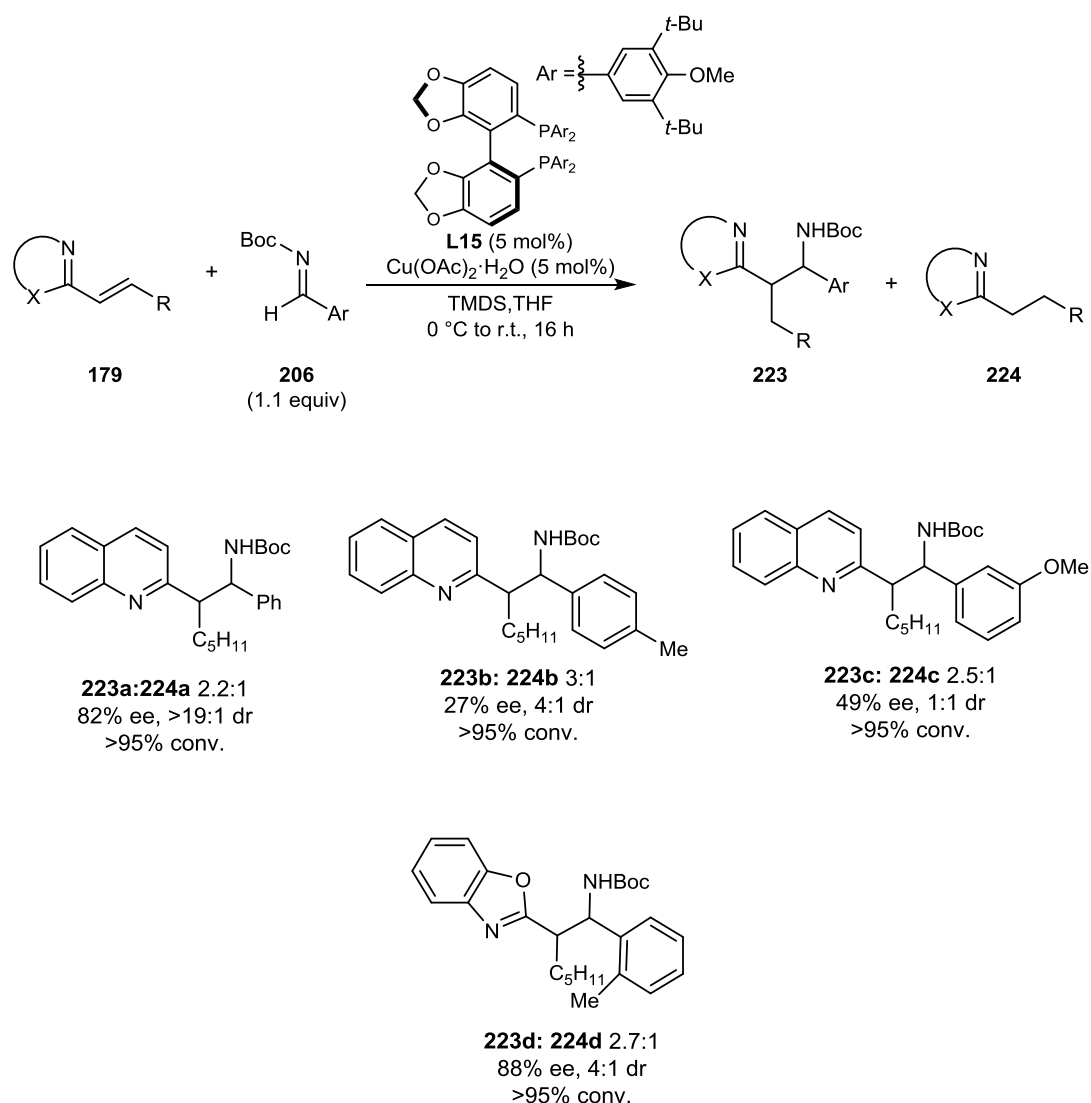
Finally the removal of the Boc group from **221a** was achieved under acidic conditions (using HCl generated by the reaction of TMSCl with MeOH), which provided the amine **222** in 90% yield with no loss of enantiopurity (Scheme 3.14).



Scheme 3.14: Deprotection of **221a**

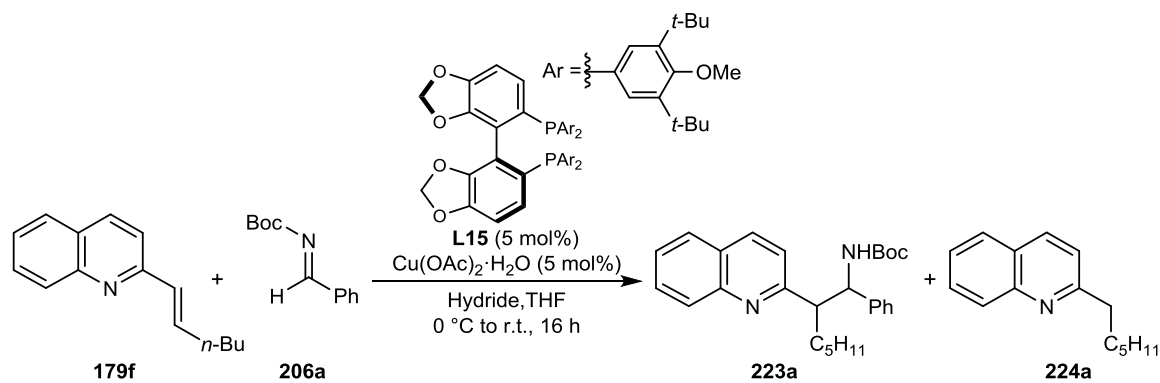
3.6 Exploration of β -Substituted Alkenylazaarenes

Initial investigations into β -substituted alkenylazaarenes were briefly explored as reductive coupling partners using conditions established for vinylazaarenes in the preceding discussions (Scheme 3.15). Initial reactions were promising; with the desired coupled product obtained with various β -substituted alkenylazaarenes and *N*-Boc imines. However, chemoselectivity between the desired coupled product **223** and the reduction product **224** was very poor. The diastereoselectivities and enantioselectivities also varied significantly.



Scheme 3.15: Reductive Coupling of β -Substituted Alkenylazaarenes with *N*-Boc Imine **206**

Using the reaction between β -substituted alkenylazaarene **179f** and *N*-Boc imine **206a**, attempts were made to improve the chemoselectivity of the reaction (Table 3.04). Increasing the equivalents of the hydride source TMDS did not result in any significant improvements in terms of chemoselectivity. Changing the hydride source to PhSiH_3 saw a slight increase in the ratio of reduction product **224a** to coupled product **223a**. Increasing the equivalents of imine **206a** to 2.5 equivalents saw an improvement in the chemoselectivity (entries 7 to 9) towards the coupled product; however, conversion was also adversely affected. Further investigations are required in this area to establish optimum reaction conditions.

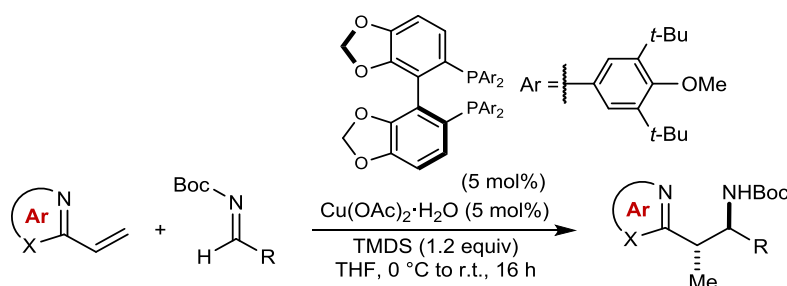
Table 3.04: Optimisation Reactions for β -Substituted Alkenylazaarene **179f**

Entry ^a	Hydride (equiv)	Imine (equiv)	Conv. (%)	223a : 224a ^b	dr ^b of 223a	ee of 223a (%) ^c
1	TMDS 1.2	1.1	>95	2.2:1	19:1	82
2	TMDS 1.4	1.1	>95	2.1:1	19:1	83
3	TMDS 1.6	1.1	>95	1.7:1	19:1	82
4	PhSiH ₃ 1.2	1.1	>95	1.7:1	19:1	82
5	PhSiH ₃ 1.4	1.1	>95	1.9:1	19:1	84
6	PhSiH ₃ 1.6	1.1	>95	1.8:1	19:1	79
7	PhSiH ₃ 1.4	1.5	>95	2.4:1	19:1	86
8	PhSiH ₃ 1.4	2.0	80	2.5:1	19:1	87
9	PhSiH ₃ 1.4	2.5	70	5: 1	19:1	84

^aReactions were conducted using 0.1 mmol of **179f**. ^bDetermined by ¹H NMR analysis of the unpurified reaction mixtures. ^cDetermined by chiral HPLC analysis.

3.7 Conclusions and Future Work

In summary, an enantioselective copper-catalysed reductive coupling of vinylazaarenes with *N*-Boc aldimines has been developed.³³ The results demonstrate the ability of chiral copper-bisphosphine complexes to catalyse the enantioselective reductive coupling of vinylazaarenes with hetero(aryl) *N*-Boc imines. The reactions provide reductive coupling products with moderate to high enantioselectivities. Compatible azaarenes included quinoline, quinoxaline, bromo-pyridine, pyridazine, benzoxazole, benzothiazole and thiazole. A range of aromatic imines were shown to be effective coupling partners with substituents at the *ortho*-, *meta*- and *para*-positions on the phenyl ring (such as methyl, chloro, trifluoromethyl or methoxy) (Scheme 3.16). Reactions of imines containing 1-naphthyl, 2-naphthyl, 2-thienyl, dioxolane or boronate esters were also successful. The reaction is also compatible with aliphatic imines. In addition, successful deprotection of the Boc-group enabled rapid synthesis of the corresponding chiral free amine with no loss of enantiopurity.



The use of β -substituted alkenylazaarenes were briefly explored and showed promising results (high enantioselectivities and diastereoselectivities obtained for some substrates). However, further screening and reaction optimisations are required to develop it into an efficient reaction.

In both projects; the enantioselective copper-catalysed reductive coupling of alkenylazaarenes with ketones and the enantioselective copper-catalysed reductive coupling of vinylazaarenes with *N*-Boc imines, stoichiometric quantities of

organosilanes were employed which creates a stoichiometric amount of silyl waste at the end of the reaction. On an industrial scale the removal of stoichiometric waste can be difficult and costly. Future work in this area could be to explore the use of molecular hydrogen (cheap, non-toxic and no stoichiometric waste formed) as the hydride source whilst still employing a cheap and earth abundant metal such as copper as catalyst.

4. EXPERIMENTAL

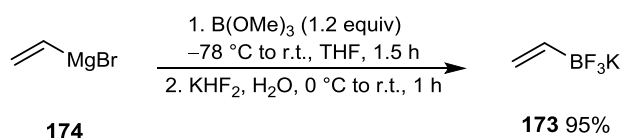
4.1 Enantioselective Copper-Catalysed Reductive Coupling of Alkenylazaarenes with Ketones

General Information

THF and toluene were dried and purified by passage through activated alumina columns using a solvent purification system. All commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien 60F₂₅₄ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using vanillin, potassium permanganate, or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.⁷⁸ Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in CHCl₃. ¹H NMR spectra were recorded on a Bruker AV500 (500 MHz), a Bruker AVA400 (400 MHz) spectrometer, or a Bruker OPEN400 (400 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard (CDCl₃ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ¹³C NMR spectra were recorded on a Bruker AV500 (125.8 MHz) spectrometer or a Bruker AVA400 (100.6 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard (CDCl₃ at 77.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. Proton-decoupled ¹⁹F NMR spectra were recorded on a Bruker AVA 400 MHz (376 MHz) spectrometer. Chemical shifts are

reported in parts per million (ppm) downfield of CFCl_3 , using fluorobenzene as internal standard ($\text{C}_6\text{H}_5\text{F}$ at -113.2 ppm). High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer or a Finnigan MAT 95XP spectrometer at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea, or on a Finnigan MAT 900 XLT spectrometer at the School of Chemistry, University of Edinburgh. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter. Chiral HPLC analysis was performed on an Agilent 1100 instrument using 4.6×250 mm columns. Authentic racemic samples of products for chiral HPLC assay determinations were obtained using *rac*-BINAP as the ligand.

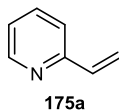
Preparation of Potassium Vinyltrifluoroborate (**173**)



To a solution of trimethyl borate (6.90 mL, 62.0 mmol) in THF (45 mL) was added dropwise vinylmagnesium bromide **174** (1.0 M THF solution, 50 mL, 50 mmol) at -78°C . The resulting suspension was stirred for 20 min at -78°C and then allowed to warm to room temperature for 1 h. The mixture was then cooled to 0°C and KHF_2 (19.0 g, 248 mmol) was added followed by the addition of water (35 mL) over 30 min. After stirring at room temperature for 20 min, the solution was concentrated and the crude material was dissolved in acetone, filtered and concentrated. The resulting white solid was purified by dissolving in hot acetone and precipitating with Et_2O , to give potassium trifluoroborate (**173**) (6.35 g, 95%) as a white solid. ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{OC}$) δ 5.83 (1H, ddq, $J_{\text{HH}} = 19.7, 13.5$ and $J_{\text{HB}} = 3.7$ Hz, $\text{CH}=\text{CH}_2$), 5.30-5.18 (1H, m, $\text{CH}=\text{CH}_2$), 5.16-5.04 (1H, m, $\text{CH}=\text{CH}_2$); ^{13}C NMR (100.6 MHz, $(\text{CD}_3)_2\text{OC}$) δ 120.6 (q, $J_{\text{CB}} = 4.6$ Hz); ^{19}F NMR (377 MHz, $(\text{CD}_3)_2\text{OC}$) δ -142.8 (dd, $J = 104.5, 46.0$ Hz). ^1H NMR, ^{13}C NMR and ^{19}F NMR data were consistent with those reported previously.⁶⁷

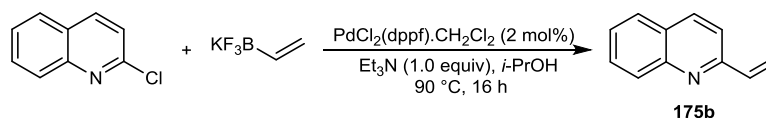
4.1.1 Preparation of Alkenylazaarenes

2-Vinylpyridine (175a)



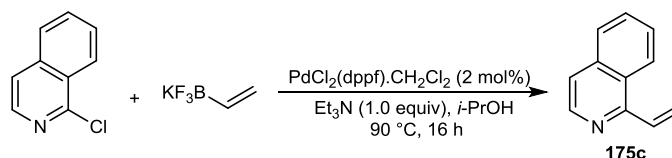
Commercially available.

2-Vinylquinoline (175b)



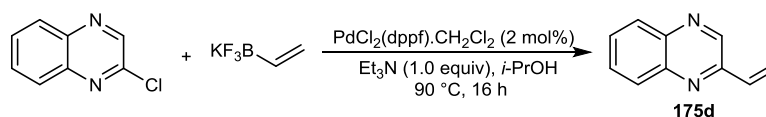
A solution of 2-chloroquinoline (1.64 g, 10.0 mmol), potassium vinyltrifluoroborate (1.61 g, 12.0 mmol), $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (163 mg, 0.200 mmol), and Et_3N (1.4 mL, 10 mmol) in *i*-PrOH (156 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH_2Cl_2 (100 mL) and H_2O (40 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2×50 mL) and the combined organic layers were washed with brine (100 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave *vinylquinoline* **175b** (1.26 g, 81%) as a pale yellow oil. ^1H NMR (500 MHz, CDCl_3) δ 8.13 (1H, d, $J = 8.6$ Hz, ArH), 8.08 (1H, d, $J = 8.5$ Hz, ArH), 7.79 (1H, d, $J = 8.1$ Hz, ArH), 7.71 (1H, ddd, $J = 8.4, 6.9, 1.4$ Hz, ArH), 7.62 (1H, d, $J = 8.6$ Hz, ArH), 7.54-7.48 (1H, m, ArH), 7.05 (1H, dd, $J = 17.4, 10.9$ Hz, $\text{CH}=\text{CH}_2$), 6.29 (1H, dd, $J = 17.4, 0.6$ Hz, $\text{CH}=\text{CH}_2$), 5.68 (1H, dd, $J = 10.9, 0.7$ Hz, $\text{CH}=\text{CH}_2$); ^{13}C NMR (125.8 MHz, CDCl_3) δ 156.1 (C), 148.0 (C), 138.0 (CH), 136.4 (CH), 129.6 (CH), 129.4 (CH), 127.48 (CH), 127.45 (C), 126.3 (CH), 119.8 (CH_2), 118.4 (CH). ^1H NMR and ^{13}C NMR data were consistent with those reported previously.⁷⁹

1-Vinylisoquinoline (175c)



A solution of 1-chloroisoquinoline (1.31 g, 8.00 mmol), potassium vinyltrifluoroborate (1.29 g, 9.60 mmol), $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ (131 mg, 0.160 mmol), and Et_3N (1.1 mL, 8.0 mmol) in $i\text{-PrOH}$ (110 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH_2Cl_2 (50 mL) and H_2O (40 mL). The aqueous layer was separated and extracted with CH_2Cl_2 ($2 \times 50\text{ mL}$) and the combined organic layers were washed with brine (50 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5%→20% EtOAc/hexane) gave *vinylisoquinoline* **175c** (812 mg, 65%) as a dark brown oil. ^1H NMR (500 MHz, CDCl_3) δ 8.54 (1H, d, $J = 5.6\text{ Hz}$, ArH), 8.27 (1H, dd, $J = 8.5, 0.7\text{ Hz}$, ArH), 7.82 (1H, d, $J = 8.2\text{ Hz}$, ArH), 7.72 – 7.56 (4H, m, ArH & CH=CH_2), 6.53 (1H, dd, $J = 17.0, 1.9\text{ Hz}$, CH=CH_2), 5.73 (1H, dd, $J = 10.8, 1.9\text{ Hz}$, CH=CH_2); ^{13}C NMR (125.8 MHz, CDCl_3) δ 154.9 (C), 142.3 (CH), 136.6 (C), 132.1 (CH), 129.9 (CH), 127.2 (CH), 127.2 (CH), 126.4 (C), 124.7 (CH), 121.8 (CH_2), 120.3 (CH). ^1H NMR and ^{13}C NMR data were consistent with those reported previously.⁸⁰

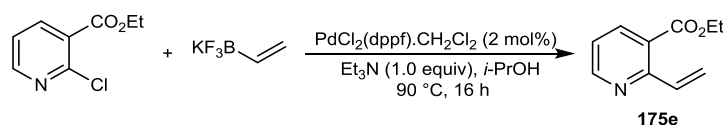
2-Vinylquinoxaline (175d)



A solution of 2-chloroquinoxaline (1.32 g, 8.00 mmol), potassium vinyltrifluoroborate (1.29 g, 9.60 mmol), $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ (131 mg, 0.160 mmol), and Et_3N (1.1 mL, 8.0 mmol) in $i\text{-PrOH}$ (125 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH_2Cl_2 (50 mL) and H_2O (40 mL). The aqueous layer was separated and extracted with CH_2Cl_2 ($2 \times 50\text{ mL}$) and the combined organic layers were washed with brine (50 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the *vinylquinoxaline* **175d** (944 mg, 76%)

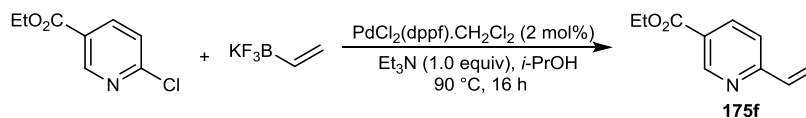
as an orange oil. ^1H NMR (500 MHz, CDCl_3) δ 9.01 (1H, s, ArH), 8.12-8.01 (2H, m, ArH), 7.77 (1H, dd, $J = 8.4, 6.9, 1.6$ Hz, ArH), 7.73 (1H, dd, $J = 8.4, 6.9, 1.8$ Hz, ArH), 7.05 (1H, dd, $J = 17.0, 11.1$ Hz, $\text{CH}=\text{CH}_2$), 6.49 (1H, dd, $J = 17.0, 0.5$ Hz, $\text{CH}=\text{CH}_2$), 5.80 (1H, dd, $J = 11.1, 0.5$ Hz, $\text{CH}=\text{CH}_2$); ^{13}C NMR (125.8 MHz, CDCl_3) δ 150.5 (C), 143.6 (CH), 142.2 (C), 141.8 (C), 134.8 (CH), 130.3 (CH), 129.5 (CH), 129.4 (CH), 129.1 (CH), 122.1 (CH_2). ^1H NMR and ^{13}C NMR data were consistent with those reported previously.⁸¹

Ethyl-2-vinyl-nicotinate (**175e**)



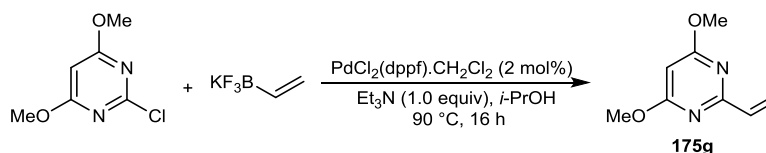
A solution ethyl-2-chloronicotinate (928 mg, 5.00 mmol), potassium vinyltrifluoroborate (804 mg, 6.00 mmol), $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ (82 mg, 0.10 mmol), and Et_3N (0.5 mL, 5.0 mmol) in *i*-PrOH (80 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH_2Cl_2 (100 mL) and H_2O (40 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2×50 mL) and the combined organic layers were washed with brine (100 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the *vinylnicotinate* **175e** (804 mg, 91%) as a dark yellow oil. IR (film) 2982, 1722 ($\text{C}=\text{O}$), 1581, 1557, 1437, 1263, 1140, 1073, 990, 940, 797, 743 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.69 (1H, dd, $J = 4.7, 1.8$ Hz, ArH), 8.15 (1H, dd, $J = 7.9, 1.8$ Hz, ArH), 7.62 (1H, dd, $J = 17.0, 10.7$ Hz, $\text{CH}=\text{H}$), 7.23 (1H, dd, $J = 7.9, 4.7$ Hz, ArH), 6.49 (1H, dd, $J = 17.0, 2.2$ Hz, $\text{CH}=\text{CH}_2$), 5.59 (1H, dd, $J = 10.7, 2.2$ Hz, $\text{CH}=\text{CH}_2$), 4.39 (2H, q, $J = 7.1$ Hz, OCH_2CH_3), 1.4 (3H, t, $J = 7.1$ Hz, OCH_2CH_3); ^{13}C NMR (125.8 MHz, CDCl_3) δ 166.4 (C), 155.0 (C), 151.9 (CH), 138.4 (CH), 133.8 (CH), 124.6 (C), 121.8 (CH), 121.4 (CH_2), 61.5 (CH_2), 14.2 (CH_3); m/z (EI) 177.1 ($[\text{M}+\text{H}]^+$, 100). ^1H and ^{13}C NMR data were consistent with those reported previously.⁸²

Ethyl 6-vinylpyridine-3-carboxylate (175f)



A solution of ethyl-6-chloronicotinate (1.48 g, 8.00 mmol), potassium vinyltrifluoroborate (1.29 g, 9.60 mmol), $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (131 mg, 0.160 mmol), and Et_3N (1.1 mL, 8.0 mmol) in $i\text{-PrOH}$ (125 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH_2Cl_2 (100 mL) and H_2O (40 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2×50 mL) and the combined organic layers were washed with brine (100 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc /hexane) gave *vinylpyridine* **175f** (1.30 g, 92%) as a pale orange oil. IR (film) 2938, 1722 ($\text{C}=\text{O}$), 1595, 1368, 1287, 1115, 1025, 856, 800, 741 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.17 (1H, d, $J = 1.8$ Hz, ArH), 8.25 (1H, dd, $J = 8.2, 2.2$ Hz, ArH), 7.40 (1H, d, $J = 8.2$ Hz, ArH), 6.87 (1H, dd, $J = 17.5, 10.8$ Hz, $\text{CH}=\text{CH}_2$), 6.34 (1H, dd, $J = 17.5, 1.0$ Hz, $\text{CH}=\text{CH}_2$), 5.62 (1H, dd, $J = 10.8, 1.0$ Hz, $\text{CH}=\text{CH}_2$), 4.41 (2H, q, $J = 7.1$ Hz, OCH_2CH_3), 1.41 (3H, t, $J = 7.1$ Hz, OCH_2CH_3); ^{13}C NMR (125.8 MHz, CDCl_3) δ 165.2 (C), 159.1 (C), 150.8 (CH), 137.6 (CH), 136.2 (CH), 124.8 (C), 120.9 (CH_2), 120.6 (CH), 61.3 (CH_2), 14.3 (CH_3); m/z (EI) 177 ($[\text{M}]^+$, 100).

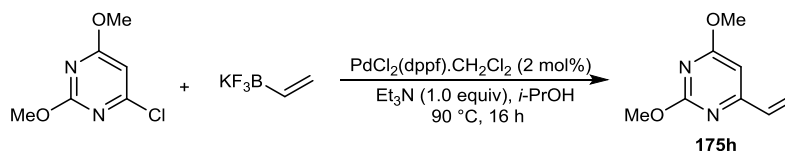
2-Vinyl-4,6-dimethoxypyrimidine (175g)



A solution of 2-chloro-4,6-methoxypyrimidine (1.40 g, 8.00 mmol), potassium vinyltrifluoroborate (1.29 g, 9.60 mmol), $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (131 mg, 0.160 mmol), and Et_3N (1.1 mL, 8.0 mmol) in $i\text{-PrOH}$ (125 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH_2Cl_2 (100 mL) and H_2O (40 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2×50 mL) and the combined organic layers were washed with brine (100 mL),

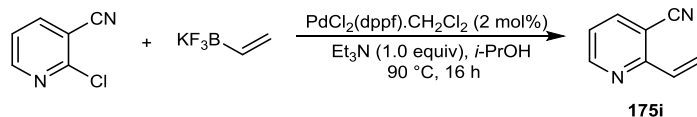
dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the *vinylpyrimidine* **175g** (1.00 g, 75%) as a pale yellow oil. IR (film) 2953, 1583, 1396, 1378, 1261, 1191, 1164, 1043, 987, 830 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.70 (1H, dd, *J* = 17.3, 10.2 Hz, CH=CH₂), 6.60 (1H, dd, *J* = 17.3, 2.2 Hz, CH=CH₂), 5.92 (1H, s, ArH), 5.68 (1H, dd, *J* = 10.2, 2.2 Hz, CH=CH₂), 3.97 (6H, s, 2 × OCH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 171.3 (2 × C), 163.3 (C), 136.5 (CH), 123.6 (CH₂), 88.0 (CH), 53.9 (2 × CH₃); HRMS (ESI) Exact mass calcd for C₈H₁₁N₂O₂ [M+H]⁺: 167.0815, found: 167.0814.

4-Vinyl-2,6-dimethoxypyrimidine (**175h**)



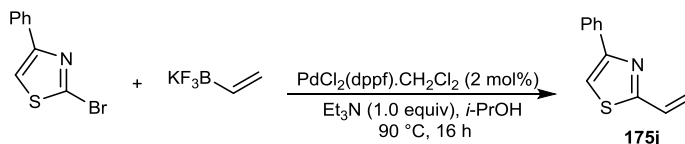
A solution of 6-chloro-2,4-dimethoxypyrimidine (1.40 g, 8.00 mmol), potassium vinyltrifluoroborate (1.29 g, 9.60 mmol), PdCl₂(dppf)·CH₂Cl₂ (131 mg, 0.160 mmol), and Et₃N (1.1 mL, 8.0 mmol) in *i*-PrOH (125 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH₂Cl₂ (100 mL) and H₂O (40 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (2 × 50 mL) and the combined organic layers were washed with brine (100 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave *vinylpyrimidine* **175h** (1.07 g, 80%) as a pale yellow oil. IR (film) 2954, 1557, 1456, 1337, 1204, 1106, 1031, 840, 791, 598 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.60 (1H, dd, *J* = 17.2, 10.4 Hz, CH=CH₂), 6.46 (1H, dd, *J* = 17.2, 1.7 Hz, CH=CH₂), 6.29 (1H, s, ArH), 5.58 (1H, dd, *J* = 10.4, 1.7 Hz, CH=CH₂), 4.02 (3H, s, OCH₃), 3.98 (3H, s, OCH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 172.4 (C), 165.3 (C), 164.1 (C), 134.7 (CH), 121.9 (CH₂), 99.3 (CH), 54.6 (CH₃), 53.9 (CH₃); HRMS (ESI) Exact mass calcd for C₈H₁₁N₂O₂ [M+H]⁺: 167.0815, found: 167.0814.

2-Vinyl-nicotitrile (175i)



A solution 2-chloro-3-pyridine carbon nitrile (1.11 g, 8.00 mmol), potassium vinyltrifluoroborate (1.29 g, 9.60 mmol), $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (131 mg, 0.160 mmol), and Et_3N (1.1 mL, 8.0 mmol) in $i\text{-PrOH}$ (125 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH_2Cl_2 (100 mL) and H_2O (40 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2×50 mL) and the combined organic layers were washed with brine (100 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave *vinylnicotitrile* **175i** as pink solid (847 mg, 81%). IR (film) 3048 (=CH), 2227 ($\text{C}\equiv\text{N}$), 1577, 1553, 1442, 1393, 1098, 982, 947, 795 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.77 (1H, dd, $J = 4.8, 1.7$ Hz, ArH), 7.93 (1H, dd, $J = 7.9, 1.8$ Hz, ArH), 7.29 (1H, dd, $J = 7.9, 4.8$ Hz, ArH), 7.20 (1H, dd, $J = 16.9, 10.7$ Hz, CH=CH), 6.67 (1H, dd, $J = 16.9, 1.9$ Hz, CH=CH₂), 5.76 (1H, dd, $J = 10.7, 1.5$ Hz, CH=CH₂); ^{13}C NMR (125.8 MHz, CDCl_3) δ 157.1 (C), 152.7 (CH), 140.4 (CH), 132.0 (CH), 123.9 (CH_2), 122.0 (CH), 116.4 (C), 107.6 (C); m/z (EI) 130.1 ($[\text{M}+\text{H}]^+$, 100).

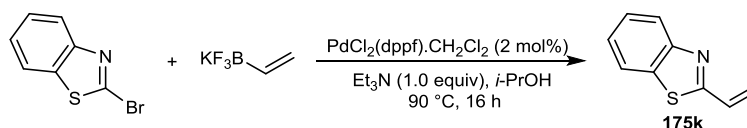
2-Vinyl-4-phenyl-1,3-thiazole (175j)



A solution of 2-bromo-4-phenylthiazole (1.92 g, 8.00 mmol), potassium vinyltrifluoroborate (1.29 g, 9.60 mmol), $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (131 mg, 0.160 mmol), and Et_3N (1.1 mL, 8.0 mmol) in $i\text{-PrOH}$ (125 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH_2Cl_2 (100 mL) and H_2O (40 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2×50 mL) and the combined organic layers were washed with brine (100 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane) gave *vinylthiazole* **175j** (1.40 g, 93%)

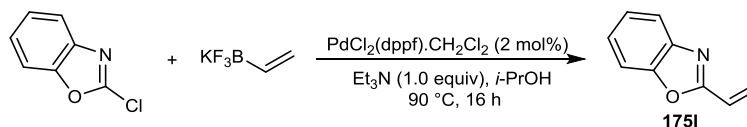
as a green solid. m.p. 28-30 °C; IR (film) 3111, 1602, 1485, 1443, 1079, 978, 919, 852, 737, 705 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.91 (2H, dt, J = 8.2, 1.6 Hz, ArH), 7.46-7.41 (2H, m, ArH), 7.40 (1H, s, ArH), 7.37-7.33 (1H, m, ArH), 7.00 (1H, ddd, J = 17.5, 10.9, 0.5 Hz, $\text{CH}=\text{CH}_2$), 6.11 (1H, d, J = 17.5 Hz, $\text{CH}=\text{CH}_2$), 5.59 (1H, d, J = 10.9 Hz, $\text{CH}=\text{CH}_2$); ^{13}C NMR (125.8 MHz, CDCl_3) δ 166.9 (C), 156.0 (C), 134.3 (C), 130.6 (CH), 128.7 (2 \times CH), 128.2 (CH), 126.4 (2 \times CH), 119.9 (CH_2), 112.3 (CH); m/z (EI) 187 ($[\text{M}]^+$, 100).

2-Vinyl-1,3-benzothiazole (175k)



A solution 2-bromobenzothiazole (1.00 g, 4.67 mmol), potassium vinyltrifluoroborate (0.75 g, 5.61 mmol), $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ (76 mg, 0.09 mmol), and Et_3N (0.65 mL, 4.67 mmol) in *i*-PrOH (60 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH_2Cl_2 (50 mL) and H_2O (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 \times 50 mL) and the combined organic layers were washed with brine (50 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave *vinylbenzothiazole* **175k** (530 mg, 70%) as a pale yellow amorphous solid. R_f 0.43 (10% EtOAc/ petroleum ether); IR (film) 3060 ($\text{CH}=\text{CH}_2$), 2359, 1489, 1437, 1312, 1108, 984, 927, 758, 728 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.01 (1H, dd, J = 7.7, 0.5 Hz, ArH), 7.86 (1H, ddd, J = 7.9, 1.1, 0.6 Hz, ArH), 7.48 (1H, ddd, J = 8.3, 7.3, 1.2 Hz, ArH), 7.39 (1H, ddd, J = 8.3, 7.3, 1.2 Hz, ArH), 7.06 (1H, dd, J = 17.5, 10.9 Hz, $\text{CH}=\text{CH}_2$), 6.20 (1H, d, J = 17.5 Hz, $\text{CH}=\text{CH}_2$), 5.78 (1H, d, J = 10.9 Hz, $\text{CH}=\text{CH}_2$); ^{13}C NMR (125.8 MHz, CDCl_3) δ 167.2 (C), 153.6 (C), 134.3 (C), 131.4 (CH), 126.3 (CH), 125.6 (CH), 123.3 (CH), 123.2 (CH_2), 121.6 (CH); HRMS (ESI) Exact mass calcd for $\text{C}_9\text{H}_8\text{NS}$ $[\text{M}+\text{H}]^+$: 162.0372, found: 162.0368.

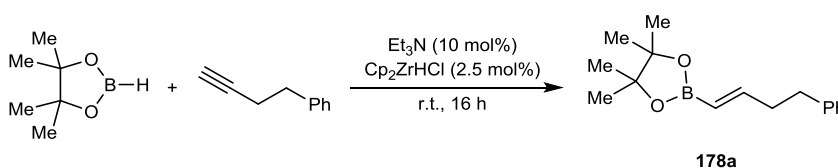
2-Vinyl-1,3-benzoxazole (175I)



A solution 2-chlorobenzoxazole (768 mg, 5.00 mmol), potassium vinyltrifluoroborate (800 mg, 6.00 mmol), $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (82 mg, 0.08 mmol), and Et_3N (0.7 mL, 5.0 mmol) in $i\text{-PrOH}$ (80 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH_2Cl_2 (50 mL) and H_2O (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2×50 mL) and the combined organic layers were washed with brine (50 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave vinylbenzoxazole **175I** (726 mg, 67%) as a colourless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.77-7.67 (1H, m, ArH), 7.56-7.47 (1H, m, ArH), 7.40-7.29 (2H, m, ArH), 6.77 (1H, dd, $J = 17.6, 11.1$ Hz, $\text{CH}=\text{CH}_2$), 6.48 (1H, dd, $J = 17.6, 1.0$ Hz, $\text{CH}=\text{CH}_2$), 5.86 (1H, dd, $J = 11.1, 1.0$ Hz, $\text{CH}=\text{CH}_2$); ^{13}C NMR (125.8 MHz, CDCl_3) δ 162.0 (C), 150.3 (C), 141.8 (C), 125.4 (CH), 125.3 (CH₂), 124.5 (CH), 123.9 (CH), 120.2 (CH), 110.5 (CH). ^1H and ^{13}C NMR data were consistent with those reported previously.⁸³

4.1.2 Preparation of Alkenylboronic Esters

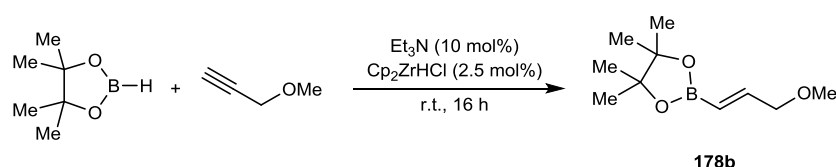
4,4,5,5-Tetramethyl-2-[(*E*)-4-phenylbut-1-enyl]-[1,3,2]dioxaborolane (**178a**)



To a mixture of 4-phenylbut-1-yne (5.62 mL, 40.0 mmol), Cp_2ZrHCl (292 mg, 1.00 mmol), and Et_3N (0.56 mL, 4.00 mmol) at room temperature was added pinacolborane (5.80 mL, 40.0 mmol) over 2 min, and the mixture was stirred for 16 h. The reaction was quenched carefully with H_2O (75 mL) and after effervescence had ceased, the mixture was extracted with Et_2O (2×100 mL). The combined organic extracts were dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the

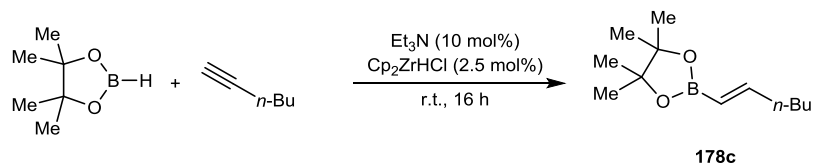
alkenylboronic ester **178a** (7.86 g, 76%) as a colourless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.39-7.35 (2H, m, ArH), 7.30-7.26 (3H, m, ArH) 6.81 (1H, dt, $J = 18.0$, 6.2 Hz, $\text{CH}=\text{CHCH}_2$), 5.61 (1H, dt, $J = 18.0$, 1.3 Hz, $\text{CH}=\text{CHCH}_2$), 2.86-2.83 (2H, m, CH_2), 2.60-2.56 (2H, m, CH_2), 1.37 (12H, s, $2 \times \text{C}(\text{CH}_3)_2$); ^{13}C NMR (125.8 MHz, CDCl_3) δ 153.4 (CH), 141.7 (C), 128.4 ($4 \times \text{CH}$), 125.8 (CH), 83.1 ($2 \times \text{C}$), 37.4 (CH_2), 34.5 (CH_2), 24.7 ($4 \times \text{CH}_3$), the CH adjacent to boron was not observed due to the quadrupolar coupling effect of ^{11}B . ^1H and ^{13}C NMR data were consistent with those observed previously.⁸⁴

2-((*E*)-3-Methoxypropenyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**178b**)



To a mixture of 3-methoxy-propyne (2.5 mL, 30 mmol), Cp_2ZrHCl (193 mg, 0.700 mmol), and Et_3N (0.4 mL, 3.0 mmol) at room temperature was added pinacolborane (4.35 mL, 30.0 mmol) over 2 min, and the mixture was stirred for 16 h. The reaction was quenched carefully with H_2O (40 mL) and after effervescence had ceased, the mixture was extracted with Et_2O (2×50 mL). The combined organic extracts were dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc /hexane) gave the *alkenylboronic ester* **178b** (2.44 g, 41%) as a colourless oil. ^1H NMR (500 MHz, CDCl_3) δ 6.68-6.57 (1H, m, $\text{CH}=\text{CH}$), 5.69 (1H, dm, $J = 18.2$ Hz, $\text{CH}=\text{CH}$), 4.00-3.99 (2H, m, CH_2), 3.34 (3H, s, OCH_3), 1.26 (12H, s, $2 \times \text{C}(\text{CH}_3)_2$); ^{13}C NMR (125.8 MHz, CDCl_3) δ 149.0 (CH), 83.2 ($2 \times \text{C}$), 74.1 (CH_2), 58.3 (CH_3), 24.7 ($4 \times \text{CH}_3$), the CH adjacent to boron was not observed due to the quadrupolar coupling effect of ^{11}B . ^1H and ^{13}C NMR data were consistent with those observed previously.⁸⁵

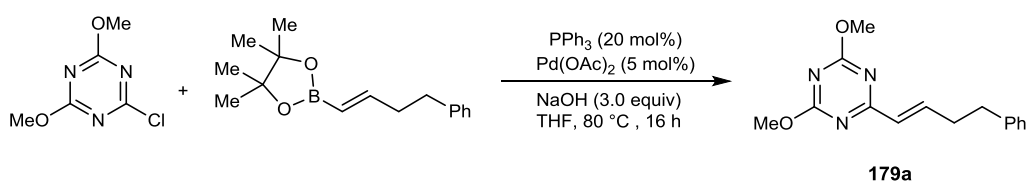
2-[(1*E*)-Hex-1-en-1-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**178c**)



To a mixture of 1-hexyne (7.30 mL, 80.0 mmol), Cp_2ZrHCl (516 mg, 2.00 mmol), and Et_3N (1.12 mL, 8.00 mmol) at room temperature was added pinacolborane (11.6 mL, 80.0 mmol) over 2 min, and the mixture was stirred for 16 h. The reaction was quenched carefully with H_2O (150 mL) and after effervescence had ceased, the mixture was extracted with Et_2O (2×100 mL). The combined organic extracts were dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc /hexane) gave the *alkenylboronic ester* **178c** (7.90 g, 47%) as a colourless oil. ^1H NMR (500 MHz, CDCl_3) δ 6.64 (1H, dt, $J = 17.9$, 6.4 Hz, $\text{CH}=\text{CHCH}_2$), 5.43 (1H, dt, $J = 17.9$, 1.6 Hz, $\text{CH}=\text{CHCH}_2$), 2.20–2.11 (2H, m, CH_2), 1.45–1.30 (4H, m, $2 \times \text{CH}_2$), 1.27 (12H, s, $2 \times \text{C}(\text{CH}_3)_2$), 0.90 (3H, t, $J = 7.1$ Hz, CH_3). ^{13}C NMR (125.8 MHz, CDCl_3) δ 154.7 (CH), 82.9 ($2 \times \text{C}$), 35.5 (CH_2), 30.3 (CH_2), 24.7 ($4 \times \text{CH}_3$), 22.2 (CH_2), 13.9 (CH_3). ^1H and ^{13}C NMR data were consistent with those observed previously.⁸⁵

4.1.3 Preparation of β -Substituted Alkenylazaarenes

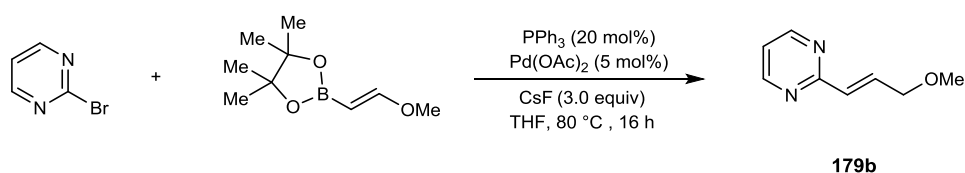
2,4-Dimethoxy-6-[(*E*)-3-methoxyprop-1-en-1-yl]-1,3,5-triazine (**179a**)



A solution of 2-chloro-4,6-dimethyl-1,3,5-triazine (1.40 g, 8.00 mmol), boronic ester **178a**⁸⁴ (2.27 g, 8.80 mmol), $\text{Pd}(\text{OAc})_2$ (269 mg, 1.20 mmol), PPh_3 (630 mg, 2.40 mmol), and NaOH (960 mg, 24.0 mmol) in THF (80 mL) was heated to reflux for 2 h. The mixture was cooled to room temperature, diluted with H_2O (60 mL), and extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were washed with brine (50 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10%→20% EtOAc /hexane) gave the

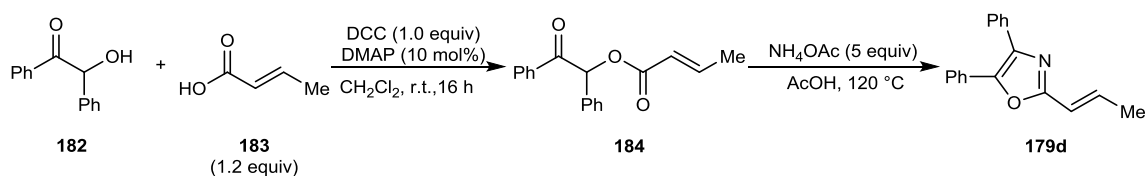
alkenyltriazine **179a** (1.41 g, 65%) as a pale brown solid. m.p. 52-54 °C; IR (film) 1654, 1559, 1498, 1458, 1352, 1201, 1111, 1082, 979, 816 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.48 (1H, dt, *J* = 15.6, 6.9 Hz, CH=CHCH₂), 7.33-7.28 (2H, m, ArH), 7.24-7.18 (3H, m, ArCH), 6.39 (1H, d, *J* = 15.6 Hz, CH=CHCH₂), 4.05 (6H, s, 2 × OCH₃), 2.88-2.81 (2H, m, CH₂Ph), 2.68-2.60 (2H, m, CH₂CH₂Ph); ¹³C NMR (125.8 MHz, CDCl₃) δ 174.6 (C), 172.5 (C), 146.3 (CH), 141.0 (C), 128.5 (2 × CH), 128.3 (2 × CH), 126.1 (CH), 55.0 (2 × CH₃), 34.6 (CH₂), 34.4 (CH₂); HRMS (ES) Exact mass calcd for C₁₅H₁₈N₃O₂ [M+H]⁺: 272.1394, found: 272.1391.

2-[(*E*)-3-Methoxyprop-1-en-1-yl]pyrimidine (**179b**)



A solution of 2-bromopyrimidine (477 mg, 3.00 mmol), alkenylboronic ester **85e** (588 μL, 2.77 mmol), Pd(OAc)₂ (34 mg, 0.15 mmol), PPh₃ (157 mg, 0.600 mmol), and Cs₂CO₃ (1.95 g, 6.00 mmol) in MeCN (30 mL) and H₂O (8 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, diluted with H₂O (30 mL), and extracted with CH₂Cl₂ (2 × 50 mL). The combined organic layers were washed with saturated aqueous NH₄Cl solution (50 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (5%→40% EtOAc/hexane) gave the *alkenylpyrimidine* **179b** (303 mg, 75%) as a yellow oil. IR (film) 1723, 1659, 1557, 1420, 1383, 1319, 1192, 1122, 977, 749 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.69 (2H, d, *J* = 4.7 Hz, ArH), 7.19 (1H, dt, *J* = 15.7, 5.7 Hz, CH=CHCH₂), 7.12 (1H, t, *J* = 4.9 Hz, ArH), 6.83-6.76 (1H, m, CH=CHCH₂), 4.21 (2H, dd, *J* = 5.2, 1.7 Hz, CH₂), 3.44 (3H, s, OCH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 164.2 (C), 157.0 (2 × CH), 137.1 (CH), 130.4 (CH), 118.8 (CH), 72.1 (CH₂), 58.4 (CH₃); HRMS (EI) Exact mass calcd for C₈H₁₀N₂O₁ [M]⁺: 150.0788, found: 150.0787.

(*E*)-4,5-Diphenyl-2-(prop-1-enyl)oxazole (**179d**)

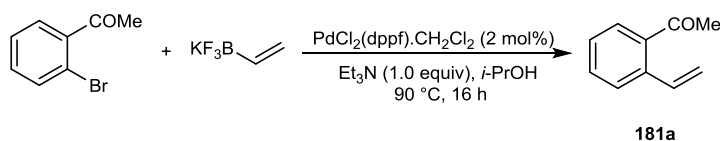


Benzoin (2.12 g, 10.0 mmol), 4-dimethylaminopyridine (122 mg, 1.00 mmol) and (E)-but-2-enoic acid (0.95 g, 11.0 mmol) were dissolved in CH₂Cl₂ (25 mL), and dicyclohexylcarbodiimide (2.06 g, 10.0 mmol) was subsequently added. The reaction was stirred at room temperature for 16 h. The reaction was diluted with EtOAc (25 mL) and vacuum filtered through a silica plug. The resulting eluent was washed with 5% HCl (50 mL), saturated NaHCO₃ (50 mL), brine (50 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (10%→20% EtOAc/hexane) gave the enoate **184** (1.52 g, 54%).

Enoate **184** (1.49 g, 5.31 mmol), ammonium acetate (2.05 g, 26.6 mmol) and acetic acid (8 mL) were heated to reflux at 120 °C for 2 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (20 mL) and washed with H₂O (2 × 20 mL). The combined organic layers were washed with saturated NaHCO₃ (50 mL), brine (50 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the alkenyloxazole **179d** (600 mg, 43%) as a white solid. ¹H NMR (500 MHz, CDCl₃) δ 7.75-7.76 (2H, m, ArH), 7.67-7.68 (2H, m, ArH), 7.32-7.43 (6H, m, ArH), 6.89 (1H, dq, *J* = 15.9, 6.9 Hz, CH=CHCH₃), 6.45 (1H, app dd, *J* = 15.9, 1.7 Hz, CH=CHCH₃), 2.02 (3H, dd, *J* = 6.9, 1.7 Hz, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 159.7 (C), 144.5 (C), 136.1 (C), 135.3 (CH), 132.5 (CH), 128.9 (CH), 128.55 (CH), 128.46 (CH), 128.3 (CH), 128.0 (2 × CH), 127.9 (2 × CH), 126.4 (CH), 117.7 (CH), 18.5 (CH₃); HRMS (ES⁺): Exact mass calcd for C₁₈H₁₅NO [M+H]⁺: 216.1232, found: 262.1230. ¹H and ¹³C NMR data were consistent with those observed previously.⁸⁶

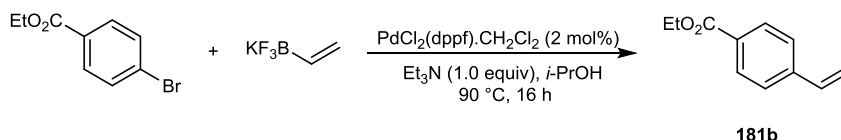
4.1.4 Preparation of Vinylarenes

2-Vinylacetophenone (181a)



A solution of 2-bromoacetophenone (0.40 mL, 3.00 mmol), potassium vinyltrifluoroborate (482 mg, 3.60 mmol), $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (49 mg, 0.06 mmol), and Et_3N (0.42 mL, 3.00 mmol) in $i\text{-PrOH}$ (50 mL) were heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH_2Cl_2 (50 mL) and H_2O (20 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2×20 mL) and the combined organic layers were washed with brine (50 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc /hexane) gave *vinylacetophenone* **181a** (847 mg, 81%) as a colourless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.64–7.56 (2H, m, ArH), 7.48–7.43 (1H, m, ArH), 7.33 (1H, dd, $J = 7.5, 1.3$ Hz, ArH), 7.21 (1H, dd, $J = 17.4, 10.9$ Hz, $\text{CH}=\text{CH}_2$), 5.65 (1H, dd, $J = 17.4, 1.3$ Hz, $\text{CH}=\text{CH}_2$), 5.36 (1H, dd, $J = 10.9, 1.3$ Hz, $\text{CH}=\text{CH}_2$), 2.59 (3H, s, CH_3). ^1H NMR data was consistent with those reported previously.⁸⁷

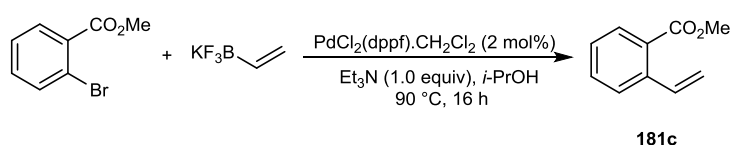
Ethyl 4-ethenylbenzoate (181b)



A solution of ethyl 4-bromobenzoate (1.3 mL, 8.0 mmol), potassium vinyltrifluoroborate (1.29 g, 9.60 mmol), $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (131 mg, 0.160 mmol), and Et_3N (1.1 mL, 8.0 mmol) in $i\text{-PrOH}$ (125 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH_2Cl_2 (100 mL) and H_2O (40 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2×50 mL) and the combined organic layers were washed with brine (100 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc /hexane) gave *ethyl benzoate* **181b** (1.13 g,

80%) as a clear colourless oil. ^1H NMR (500 MHz, CDCl_3) δ 8.05-7.99 (2H, m, ArH), 7.49-7.44 (2H, m, ArH), 6.76 (1H, dd, $J = 17.6, 10.9$ Hz, CH=CH₂), 5.87 (1H, dd, $J = 17.6, 0.5$ Hz, CH=CH₂), 5.39 (1H, dd, $J = 10.9, 0.5$ Hz, CH=CH₂), 4.38 (2H, q, $J = 7.1$ Hz, CH₂CH₃), 1.41 (3H, t, $J = 7.1$ Hz, CH₂CH₃); ^{13}C NMR (125.8 MHz, CDCl_3) δ 166.4 (C), 141.8 (C), 136.1 (2 \times CH), 129.8 (2 \times CH), 129.6 (C), 126.1 (CH), 116.4 (CH₂), 60.9 (CH₂), 14.3 (CH₃). ^1H NMR and ^{13}C NMR data were consistent with those reported previously.⁸⁸

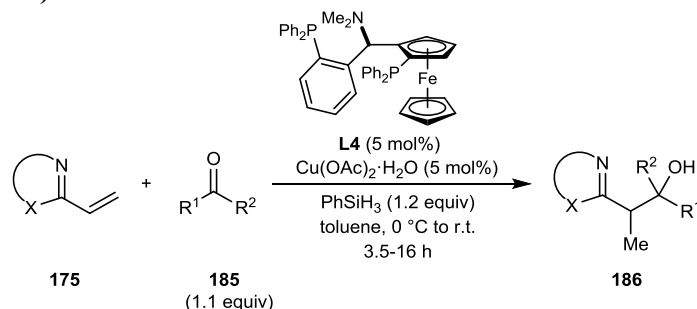
Methyl 2-vinylbenzoate (**181c**)



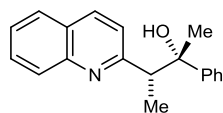
A solution of methyl-2-bromobenzoate (1.1 mL, 8.0 mmol), potassium vinyltrifluoroborate (1.29 g, 9.60 mmol), $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ (131 mg, 0.160 mmol), and Et_3N (1.1 mL, 8.0 mmol) in *i*-PrOH (125 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and partitioned between CH_2Cl_2 (100 mL) and H_2O (40 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 \times 50 mL) and the combined organic layers were washed with brine (100 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/hexane) gave *methyl benzoate* **181c** (1.10 g, 85%) as a clear colourless oil. ^1H NMR (500 MHz, CDCl_3) δ 7.89 (1H, dd, $J = 7.8, 1.4$ Hz, ArH), 7.59 (1H, dd, $J = 7.8, 0.6$ Hz, ArH), 7.52-7.44 (2H, m, ArH and CH=CH₂), 7.35-7.31 (1H, m, ArH), 5.66 (1H, dd, $J = 17.5, 1.3$ Hz, CH=CH₂), 5.37 (1H, dd, $J = 11.0, 1.3$ Hz, CH=CH₂), 3.92 (3H, s, CH₃); ^{13}C NMR (125.8 MHz, CDCl_3) δ 167.8 (C), 139.6 (C), 135.9 (CH), 132.1 (CH), 130.3 (CH), 128.6 (C), 127.4 (CH), 127.2 (CH), 116.5 (CH₂), 52.1 (CH₃). ^1H NMR and ^{13}C NMR data were consistent with those reported previously.⁸⁹

4.1.5 Enantioselective Copper-Catalysed Reductive Coupling Reactions

General Procedure: Reductive Coupling of Vinylazaarenes Using Ligand L13 (0.40 mmol Scale)

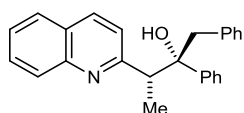


A solution of the appropriate vinylazaarene (0.40 mmol), $\text{Cu}(\text{OAc})_2\cdot\text{H}_2\text{O}$ (4.0 mg, 0.02 mmol), ligand SL-T001-1 (**L4**) (13.8 mg, 0.02 mmol), and the appropriate ketone (0.44 mmol) in toluene (2 mL) was stirred at 0 °C for 15 min. PhSiH_3 (59 μL , 0.48 mmol) was then added dropwise over 1 min. The mixture was stirred at 0 °C for 30 min, then at room temperature for 15 h. The reaction was quenched carefully with silica gel (*ca.* 250 mg), and the resulting suspension was stirred for 15 min before being filtered through a short plug of silica gel using EtOAc (50 mL) as eluent. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography to give the reductive coupling product.



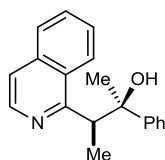
(2*S*,3*R*)-2-Phenyl-3-(quinolin-2-yl)butan-2-ol (186b). The title compound was prepared according to General Procedure from 2-vinylquinoline **175b** (62 mg, 0.40 mmol) and acetophenone (51 μL , 0.44 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a white solid (66 mg, 60%). m.p. 108-110 °C; $[\alpha]_{\text{D}}^{24} +14.2$ (*c* 0.84, CHCl_3); IR (film) 3312 (OH), 1598, 1558, 1504, 1456, 1412, 1065, 843, 762, 697 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.17 (1H, d, $J = 8.4$ Hz, ArH), 8.08 (1H, d, $J = 8.5$ Hz, ArH), 7.84 (1H, d, $J = 8.0$ Hz, ArH), 7.77-7.73 (1H, m, ArH), 7.62 (2H, d, $J = 7.4$ Hz, ArH), 7.58-7.53 (1H, m, ArH), 7.41 (2H, t, $J = 7.8$ Hz, ArH), 7.36 (1H, d, $J = 8.4$ Hz, ArH), 7.30-7.26 (1H, m, ArH), 7.06 (1H, br s, OH), 3.36 (1H, q, $J = 7.1$ Hz, CHCH_3), 1.41 (3H, s, CH_3COH), 1.13 (3H, d, $J = 7.1$ Hz, CHCH_3); ^{13}C NMR (125.8 MHz, CDCl_3) δ 166.1 (C), 147.4 (C), 146.9 (C), 137.1 (CH), 129.9 (CH),

128.8 (CH), 128.0 (2 × CH), 127.6 (CH), 126.9 (C), 126.22 (CH), 126.18 (CH), 125.0 (2 × CH), 122.5 (CH), 76.4 (C), 50.7 (CH), 30.8 (CH₃), 17.1 (CH₃); HRMS (ESI) Exact mass calcd for C₁₉H₂₀N₁O₁ [M+H]⁺: 278.1539, found: 278.1541. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r (minor) = 12.6 min, t_r (major) = 20.3 min; 93% ee.



(2*S*,3*R*)-1,2-Diphenyl-3-(quinolin-2-yl)butan-2-ol (186c). The

title compound was prepared according to General Procedure from 2-vinylquinoline **175b** (62 mg, 0.40 mmol) and 2-phenylacetophenone (86 mg, 0.44 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a white solid (85 mg, 60%). m.p. 108-110 °C; [α]_D²⁴ +55.2 (*c* 1.05, CHCl₃); IR (film) 3302 (OH), 1599, 1504, 1452, 1424, 1327, 1074, 832, 754, 700 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.22 (1H, d, *J* = 8.4 Hz, ArH), 8.13 (1H, d, *J* = 8.5 Hz, ArH), 7.87 (1H, d, *J* = 8.1 Hz, ArH), 7.78 (1H, ddd, *J* = 8.4, 6.9, 1.3 Hz, ArH), 7.61-7.56 (1H, m, ArH), 7.47-7.40 (3H, m, ArH), 7.36-7.27 (3H, m, ArH and OH), 7.25-7.20 (1H, m, ArH), 7.02-6.98 (3H, m, ArH), 6.70 (2H, dd, *J* = 6.4, 3.1 Hz, ArH), 3.60 (1H, q, *J* = 7.1 Hz, CHCH₃), 3.10 (1H, d, *J* = 13.4 Hz, CH₂Ph), 2.90 (1H, d, *J* = 13.4 Hz, CH₂Ph), 1.17 (3H, d, *J* = 7.1 Hz, CHCH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 166.2 (C), 146.8 (C), 144.5 (C), 137.5 (C), 137.3 (CH), 130.5 (2 × CH), 130.0 (CH), 128.7 (CH), 127.6 (4 × CH), 127.1 (2 × CH), 126.8 (C), 126.3 (CH), 126.1 (CH), 125.9 (CH), 125.6 (CH), 122.7 (CH), 79.6 (C), 49.0 (CH), 48.9 (CH₂), 17.5 (CH₃); HRMS (ESI) Exact mass calcd for C₂₅H₂₄N₁O₁ [M+H]⁺: 354.1852, found: 354.1856. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (99:1 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r (major) = 10.9 min, t_r (minor) = 12.4 min; 97% ee.

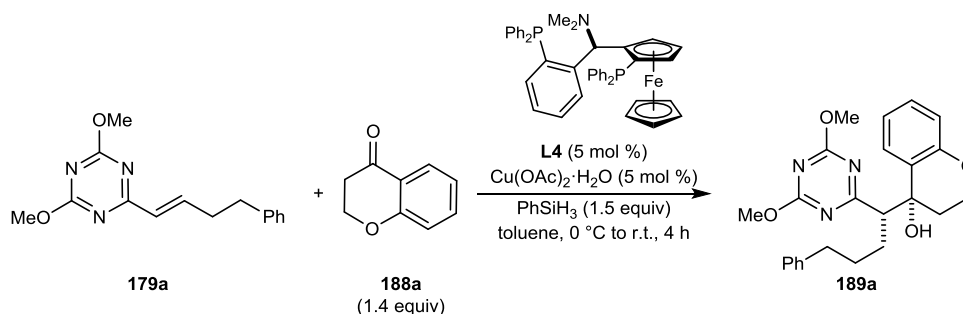


(2*R*,3*S*)-3-(Isoquinolin-1-yl)-2-phenylbutan-2-ol (186d). The title

compound was prepared according to General Procedure from 2-vinylisoquinoline **175c** (62 mg, 0.40 mmol) and acetophenone (51 μL, 0.44 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a white solid (84 mg, 76%). m.p 72-74 °C; [α]_D²⁴ -111.9 (*c*

0.97, CHCl₃); IR (film) 3290 (OH), 1561, 1502, 1457, 1385, 1065, 1002, 824, 768, 744 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.48 (1H, d, *J* = 5.7 Hz, ArH), 8.29 (1H, d, *J* = 8.5 Hz, ArH), 7.89 (1H, d, *J* = 8.1 Hz, ArH), 7.77-7.65 (4H, m, ArH), 7.61 (1H, d, *J* = 5.7 Hz, ArH), 7.49 (1H, br s, OH), 7.44 (2H, t, *J* = 7.8 Hz, ArH), 7.33-7.28 (1H, m, ArH), 4.12 (1H, q, *J* = 7.0 Hz, CHCH₃), 1.38 (3H, s, CH₃COH), 1.13 (3H, d, *J* = 7.0 Hz, CHCH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 165.8 (C), 147.8 (C), 140.4 (CH), 136.6 (C), 130.3 (CH), 128.0 (2 × CH), 127.8 (CH), 127.6 (CH), 127.1 (C), 126.2 (CH), 125.1 (2 × CH), 124.5 (CH), 119.5 (CH), 76.4 (C), 43.8 (CH), 30.5 (CH₃), 16.9 (CH₃); HRMS (ESI) Exact mass calcd for C₁₉H₂₀N₁O₁ [M+H]⁺: 278.1539, found: 278.1542. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 °C); *t*_r (major) = 9.4 min, *t*_r (minor) = 16.6 min; 90% ee.

(*R*)-4-[(*R*)-1-(4,6-Dimethoxy-[1,3,5]triazin-2-yl)-4-phenylbutyl]chroman-4-ol (189a).



A solution of alkenylazaarene **179a** (77 mg, 0.30 mmol), Cu(OAc)₂·H₂O (3.0 mg, 0.015 mmol), ligand SL-T001-1 (**L4**) (10.3 mg, 0.015 mmol), and 4-chromanone (62 mg, 0.42 mmol) in toluene (1.5 mL) was stirred at 0 °C for 15 min. PhSiH₃ (56 μL, 0.45 mmol) was then added dropwise over 1 min. The mixture was stirred at 0 °C for 30 min, then at room temperature for 4 h. The reaction was quenched carefully with silica gel (*ca.* 250 mg), and the resulting suspension was stirred for 15 min before being filtered through a short plug of silica gel using EtOAc (50 mL) as eluent. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (10%→40% EtOAc/hexane) to give a yellow gum (95 mg, 75%). [α]_D²⁴ +8.6 (*c* 0.93, CHCl₃); IR (film) 3383 (OH), 2966, 1559, 1502, 1452, 1360, 1222, 1110, 754, 446 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.33 (1H, dd, *J* =

7.9, 1.4 Hz, ArH), 7.25-7.10 (4H, m, ArH), 7.05 (2H, d, $J = 7.0$ Hz, ArH), 6.93-6.88 (1H, m, ArH), 6.86 (1H, dd, $J = 8.2, 1.1$ Hz, ArH), 4.39 (1H, br s, OH), 4.26-4.15 (2H, m, OCH₂), 4.02 (6H, s, 2 x OCH₃), 3.53 (1H, dd, $J = 11.3, 2.1$ Hz, CHCH₂), 2.55 (1H, ddd, $J = 14.8, 9.1, 6.2$ Hz, PhCH_AH_B), 2.50-2.40 (1H, m, PhCH_AH_B), 2.32 (1H, ddd, $J = 14.5, 10.2, 4.4$ Hz, OCH₂CH_XH_Y), 2.18-2.05 (1H, m, OCH₂CH_XH_Y), 1.83 (1H, ddd, $J = 14.3, 4.9, 2.9$ Hz, PhCH₂CH₂CH₂), 1.59-1.40 (2H, m, PhCH₂CH₂CH₂), 1.35-1.24 (1H, m, PhCH₂CH₂CH₂); ¹³C NMR (125.8 MHz, CDCl₃) δ 182.7 (C), 171.8 (C), 155.1 (C), 141.8 (C), 129.0 (CH), 128.1 (4 x CH), 126.5 (C), 125.8 (CH), 125.6 (CH), 120.8 (CH), 117.4 (CH), 70.7 (C), 62.6 (CH₂), 55.9 (CH), 55.2 (2 x CH₃), 35.4 (CH₂), 32.0 (CH₂), 29.8 (CH₂), 28.0 (CH₂); HRMS (ESI) Exact mass calcd for C₂₄H₂₇N₃O₄Na [M+Na]⁺: 444.1894, found: 444.1895. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 °C); t_r (minor) = 27.4 min, t_r (major) = 30.8 min; 96% ee.

4.2 Enantioselective Copper-Catalysed Reductive Coupling of Vinylazaarenes with *N*-Boc Aldimines

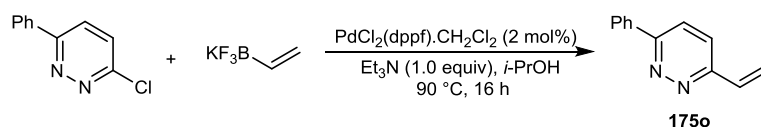
General Information

THF used in reactions were dried and purified by passage through activated alumina columns using a solvent purification system. "Petroleum ether" refers to Sigma Aldrich product 24587 (petroleum ether boiling point 40-60 °C). All commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien 60F₂₅₄ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using vanillin, potassium permanganate, or ninhydrin solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron). Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in CHCl₃. ¹H NMR spectra were recorded on a Bruker AV500 (500 MHz), a Bruker

AVA400 (400 MHz) spectrometer, or a Bruker OPEN400 (400 MHz) spectrometer. For ^1H NMR spectra, chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard (CDCl_3 at 7.27 ppm, $(\text{CD}_3)_2\text{CO}$ at 2.05 ppm, CD_3OD at 3.31 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), quin (quartet), app (apparent), br (broad). Coupling constants (J) are quoted to the nearest 0.1 Hz. For ^{13}C NMR spectra, chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard (CDCl_3 at 77.0 ppm, $(\text{CD}_3)_2\text{CO}$ at 29.84 ppm, CD_3OD at 49.00 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135° . Proton-decoupled ^{19}F NMR spectra were recorded on a Bruker AVA400 (377 MHz) spectrometer. High-resolution mass spectra were recorded using electrospray ionization (ESI) or electron impact ionization (EI) techniques. Optical rotations were performed on a Bellingham and Stanley ADP410 polarimeter. HPLC analysis was performed on Agilent 1100 or Agilent 1200 series instruments using 4.6 x 250 mm columns. Authentic racemic samples of products for chiral HPLC assay determinations were obtained using *rac*-BINAP as the ligand.

4.2.1 Preparation of Vinylazaarenes

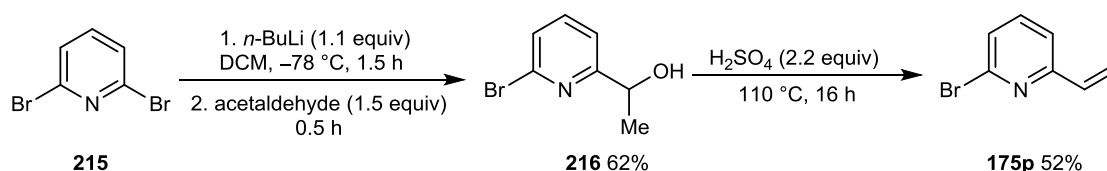
3-Phenyl-6-vinylpyridazine (175o)



A solution of 3-chloro-6-phenylpyridazine (1.53 g, 8.03 mmol), potassium vinyltrifluoroborate (1.29 g, 9.63 mmol), $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ (131 mg, 0.160 mmol), and Et_3N (1.1 mL, 7.9 mmol) in *i*-PrOH (130 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature and the solvent was removed *in vacuo*. The crude residue was dissolved CH_2Cl_2 (50 mL) and washed with H_2O (40 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2×50 mL) and the combined organic layers were washed with brine (100 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. Purification of the residue by column

chromatography (10%→20% EtOAc/*iso*-hexane) gave the *vinylazaarene* **175o** (967 mg, 66%) as a pale yellow crystalline solid. R_f 0.22 (20% EtOAc/petroleum ether); m.p 99-101 °C (EtOAc/petroleum ether); IR (CHCl₃) 3010, 1597, 1453, 1422, 1400, 1267, 1055, 1008, 943, 851 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.12-8.08 (2H, m, ArH), 7.82 (1H, d, J = 8.9 Hz, ArH), 7.62 (1H, d, J = 8.9 Hz, ArH), 7.56-7.45 (3H, m, ArH), 7.09 (1H, dd, J = 17.8, 11.0 Hz, CH=CH₂), 6.29 (1H, d, J = 17.8 Hz, CH=CH₂), 5.69 (1H, d, J = 11.1 Hz, CH=CH₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 157.8 (C), 156.5 (C), 136.1 (C), 134.3 (CH), 129.9 (CH), 128.9 (2 × CH), 126.9 (2 × CH), 123.79 (CH), 123.75 (CH), 120.2 (CH₂); HRMS (ESI) Exact mass calcd for C₁₂H₁₁N₂ [M+H]⁺: 183.0917, found: 183.0918.

2-Bromo-6-vinylpyridine (**175p**)



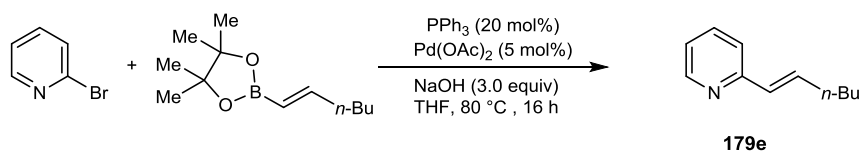
A solution of 2,6-dibromopyridine (**215**) (9.48 g, 40.0 mmol) and dry CH₂Cl₂ (125 mL) was cooled to -78 °C. *n*-BuLi in hexane (17.8 mL, 44.0 mmol, 2.5 M) was added dropwise over a period of 15 minutes. After 1 h acetaldehyde (3.40 mL, 60.0 mmol) was added over a period of 5 minutes and the reaction was allowed to stir for 30 minutes at -78 °C before it was warmed to room temperature. Saturated NH₄Cl (100 mL) was added and the reaction mixture was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic phases were washed with brine (2 × 50 mL), dried (MgSO₄) and filtered before concentrating *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane) gave the *alcohol* **216** (4.97 g, 62%) as a brown syrup that displayed spectroscopic data consistent with those reported previously.⁶⁶ ¹H NMR (500 MHz, CDCl₃) δ 7.56 (1H, t, J = 7.7 Hz, ArH), 7.39 (1H, d, J = 7.8 Hz, ArH), 7.32-7.25 (1H, m, ArH), 4.88 (1H, q, J = 6.6 Hz, CH), 3.42 (1H, br, s, OH), 1.51 (3H, d, J = 6.6 Hz, CH₃); ¹³C NMR (126 MHz, CDCl₃) δ 165.2 (C), 141.1 (C), 139.1 (CH), 126.6 (CH), 118.5 (CH), 69.1 (CH), 24.1 (CH₃).

Alcohol **216** (3.16 g, 15.6 mmol) was cooled to 0 °C and concentrated H₂SO₄ (20.0 mL, 35.0 mmol) was added slowly. The reaction was purged with N₂ before heating to 110 °C for 16 h. The reaction mixture was cooled 0 °C and solid NaOH was added

until the solution was neutral. Solids were removed by filtration and the aqueous solution extracted with diethyl ether (3×50 mL) the combined organic extracts were washed with brine (2×50 mL), dried (MgSO_4), filtered and concentrated *in vacuo*. Purification of the residue by column chromatography (5% EtOAc/*iso*-hexane) gave the *vinylazaarene* **175p** (1.49 g, 52%) as a pale yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.48 (1H, t, $J = 7.7$ Hz, ArH), 7.32 (1H, dd, $J = 7.8, 0.8$ Hz, ArH), 7.25 (1H, dd, $J = 7.8, 0.8$ Hz, ArH), 6.72 (1H, dd, $J = 17.4, 10.8$ Hz, CH=CH₂), 6.23 (1H, dd, $J = 17.4, 1.0$ Hz, CH=CH₂), 5.53 (1H, dd, $J = 10.8, 1.0$ Hz, CH=CH₂); ^{13}C NMR (100.6 MHz, CDCl_3) δ 156.9 (C), 141.9 (C), 138.7 (CH), 135.3 (CH), 126.6 ($2 \times$ CH), 119.9 (CH₂). ^1H NMR and ^{13}C NMR data were consistent with those reported previously.⁶⁶

4.2.2 Preparation of β -Substituted Alkenylazaarenes

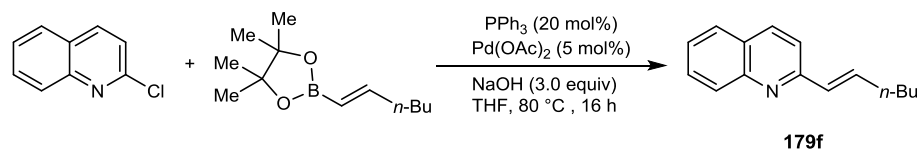
2-[(1*E*)-Hex-1-en-1-yl]pyridine (**179e**)



A solution of 2-bromopyridine (0.48 mL, 5.00 mmol), *alkenylboronic ester* **178c** (1.16 g, 5.50 mmol), $\text{Pd}(\text{OAc})_2$ (56 mg, 0.25 mmol), PPh_3 (262 mg, 1.00 mmol), and NaOH (0.6 g, 15.0 mmol) in THF (50 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et_2O (100 mL) and H_2O (50 mL). The aqueous layer was separated and extracted with Et_2O (2×30 mL) and the combined organic layers were washed with saturated aqueous NH_4Cl solution (80 mL), dried (MgSO_4), filtered and concentrate *in vacuo*. Purification of the residue by flash column chromatography (10% EtOAc/hexanes) gave the *alkenylazaarene* **179e** (801 mg, 99%) as a pale yellow liquid. ^1H NMR (400 MHz, CDCl_3) δ 8.54-8.48 (1H, m, ArH), 7.60-7.53 (1H, m, ArH), 7.24-7.18 (1H, m, ArH), 7.08-7.02 (1H, m, ArH), 6.78-6.68 (1H, m, CH=CH), 6.47 (1H, d, $J = 15.6$ Hz, CH=CH), 2.29-2.22 (2H, m, CH₂), 1.53-1.43 (2H, m, CH₂), 1.42-1.32 (2H, m, CH₂), 0.91 (3H, t, $J = 7.3$ Hz, CH₃); ^{13}C NMR (126 MHz, CDCl_3) δ 156.1 (C), 149.3 (CH),

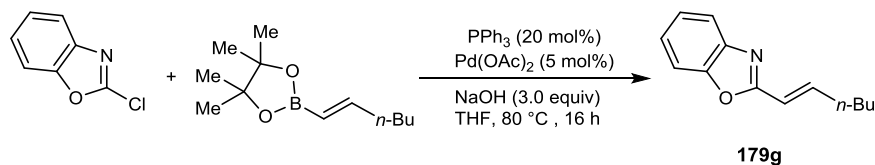
136.3 (CH), 136.0 (CH), 129.7 (CH), 121.4 (CH), 120.8 (CH), 32.4 (CH₂), 31.0 (CH₂), 22.2 (CH₂), 13.9 (CH₃); HRMS (ESI) Exact mass calcd for C₁₁H₁₆N [M+H]⁺: 162.1277, found: 162.1295.

2-[(1E)-Hex-1-en-1-yl]quinoline (179f)



A solution of 2-chloroquinoline (818 mg, 5.00 mmol), *alkenylboronic ester* **178c** (1.16 g, 5.50 mmol), Pd(OAc)₂ (56 mg, 0.25 mmol), PPh₃ (262 mg, 1.00 mmol) and NaOH (0.6 g, 15.0 mmol) in THF (50 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et₂O (100 mL) and H₂O (50 mL). The aqueous layer was separated and extracted with Et₂O (2 × 30 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl solution (80 mL), dried (MgSO₄), filtered and concentrate *in vacuo*. Purification of the residue by flash column chromatography (10% EtOAc/hexanes) gave the *alkenylazaarene* **179f** (904 mg, 86%) as an orange liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.04 (2H, dd, *J* = 8.5, 4.2 Hz, ArH), 7.74 (1H, d, *J* = 8.1 Hz, ArH), 7.71-7.63 (1H, m, ArH), 7.52 (1H, d, *J* = 8.6 Hz, ArH), 7.48-7.42 (1H, m, ArH), 6.83 (1H, dt, *J* = 15.9, 6.7 Hz, ArCH=CH), 6.72 (1H, dt, *J* = 15.9, 1.1 Hz, ArCH=CH), 2.38-2.30 (2H, m, CH₂), 1.59-1.49 (2H, m, CH₂), 1.48-1.35 (2H, m, CH₂), 0.97 (3H, t, *J* = 7.3 Hz, CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 156.5 (C), 148.0 (C), 138.0 (CH), 136.1 (CH), 131.0 (CH), 129.5 (CH), 129.1 (CH), 127.4 (CH), 127.1 (C), 125.8 (CH), 118.6 (CH), 32.7 (CH₂), 31.0 (CH₂), 22.3 (CH₂), 13.9 (CH₃). ¹H NMR and ¹³C NMR data were consistent with those reported previously.⁹⁰

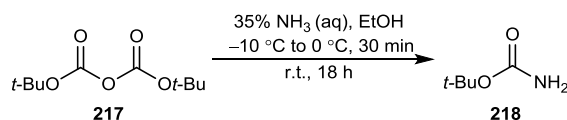
2-[(1E)-Hex-1-en-1-yl]-1,3-benzoxazole (179g)



A solution of 2-chlorobenzoxazole (0.65 mL, 5.00 mmol), *alkenylboronic ester* **178c** (1.16 g, 5.50 mmol), Pd(OAc)₂ (56 mg, 0.25 mmol), PPh₃ (262 mg, 1.00 mmol) and NaOH (600 mg, 15.0 mmol) in THF (50 mL) was heated to reflux for 16 h. The mixture was cooled to room temperature, and partitioned between Et₂O (100 mL) and H₂O (50 mL). The aqueous layer was separated and extracted with Et₂O (2 × 30 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl solution (80 mL), dried (MgSO₄), filtered and concentrate *in vacuo*. Purification of the residue by flash column chromatography (5% EtOAc/hexanes) gave the *alkenylazaarene* **179g** (530 mg, 52%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.74-7.64 (1H, m, ArH), 7.53-7.43 (1H, m, ArH), 7.35-7.30 (2H, m, ArH), 7.06 (1H, dt, *J* = 15.9, 7.2 Hz, ArCH=CH), 6.45 (1H, dt, *J* = 15.9, 1.5 Hz, ArCH=CH), 2.35 (2H, qd, *J* = 7.2, 1.5 Hz, CH₂), 1.59-1.48 (2H, m, CH₂), 1.47-1.35 (2H, m, CH₂), 0.95 (3H, t, *J* = 7.3 Hz, CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 162.6 (C), 150.3 (C), 144.4 (CH), 141.9 (C), 124.8 (CH), 124.3 (CH), 119.7 (CH), 116.7 (CH), 110.2 (CH), 32.7 (CH₂), 30.5 (CH₂), 22.2 (CH₂), 13.9 (CH₃); HRMS (ESI) Exact mass calcd for C₁₃H₁₅NNaO [M+Na]⁺: 224.1046, found: 224.1044.

4.2.3 Preparation of *N*-Boc Imines

tert-Butyl carbamate (**218**)

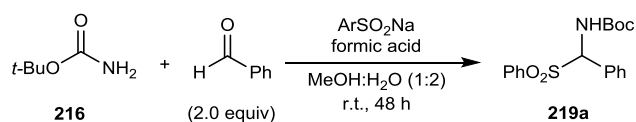


To a solution of di-*tert*-butyl dicarbonate (50.9 g, 233 mmol) in EtOH (500 mL) at –10 °C was added 35% NH₃ (aq) (50 mL) over 5 min. The reaction mixture was stirred vigorously for a further 30 min at –10 °C to 0 °C, and then at room temperature for 18 h. The solvents were removed from the resulting thick suspension *in vacuo* at 50 °C to ensure decomposition of ammonium *tert*-butyl carbonate. The residue was suspended in hexane (500 mL), stirred at 60 °C for 1 h, and then recrystallized from refluxing hexane (total volume ~650 mL) to provide *tert*-butyl carbamate (**218**) (25.9 g, 95%) as a white crystalline solid. ¹H NMR (400 MHz, CDCl₃) δ 1.47 (9H, s, C(CH₃)₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 156.5 (C), 79.5 (C), 28.2 (3 × CH₃); HRMS (ESI) Exact mass calcd for C₅H₁₁NNaO₂ [M+Na]⁺:

140.0682, found: 140.0683. ^1H NMR and ^{13}C NMR data were consistent with those reported previously.⁹¹

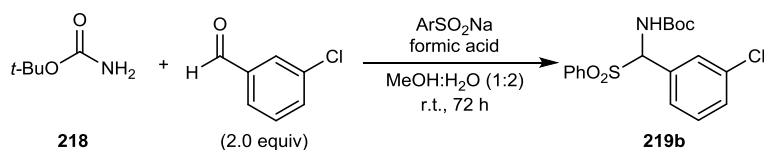
4.2.3.1 *tert*-Butyl *N*-[(benzenesulfonyl)(phenyl)methyl]carbamates

tert-Butyl *N*-[(benzenesulfonyl)(phenyl)methyl]carbamate (**219a**)



Benzaldehyde (2.30 ml, 22.5 mmol) was suspended in 2:1:0.7 H₂O:MeOH:HCO₂H (40 ml). Sodium benzenesulfinate (4.93 g, 30.0 mmol) and *tert*-butyl carbamate (**218**) (1.76 g, 15.0 mmol) were added sequentially and the reaction mixture was stirred for 2 days. The solids were collected by filtration and triturated with H₂O and then Et₂O to yield title compound as a white solid (3.94 g, 76%). ^1H NMR (400 MHz, CDCl₃) δ 7.93 (2H, d, J = 9.5 Hz, ArH), 7.69-7.62 (1H, m, ArH), 7.58-7.51 (2H, m, ArH), 7.50-7.39 (5H, m, ArH), 5.96 (1H, d, J = 10.7 Hz, NH), 5.85 (1H, d, J = 10.7 Hz, CH), 1.28 (9H, s, C(CH₃)₃); ^{13}C NMR (100.6 MHz, CDCl₃) δ 153.3 (C), 136.9 (C), 133.9 (CH), 129.9 (2 \times CH), 129.8 (C), 129.4 (2 \times CH), 129.0 (2 \times CH), 128.9 (CH), 128.7 (2 \times CH), 81.2 (C), 73.9 (CH), 28.0 (3 \times CH₃); HRMS (ESI) Exact mass calcd for C₁₈H₂₁NO₄SNa [M+Na]⁺: 370.1083, found: 370.1072. ^1H NMR and ^{13}C NMR data were consistent with those reported previously.^{10e}

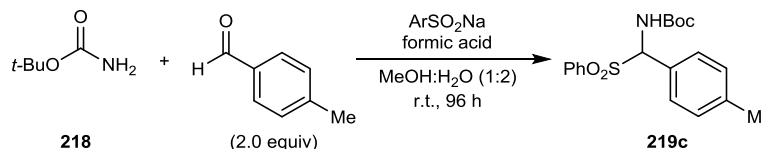
tert-Butyl *N*-[(benzenesulfonyl)(3-chlorophenyl)methyl]carbamate (**219b**)



3-Chlorobenzaldehyde (3.1 mL, 15.0 mmol) was suspended in 2:1:0.7 H₂O/MeOH/HCO₂H (40 mL). Sodium benzenesulfinate (4.92 g, 30.0 mmol) and *tert*-butyl carbamate (**218**) (1.76 g, 15.0 mmol) were added sequentially and the reaction mixture was stirred for 3 days. The solids were collected by filtration and triturated with H₂O and then Et₂O to yield the title compound as a white solid (4.64 g, 82%). ^1H NMR δ (400 MHz, CDCl₃) 7.93 (2H, d, J = 7.4 Hz, ArH), 7.67 (1H, t, J

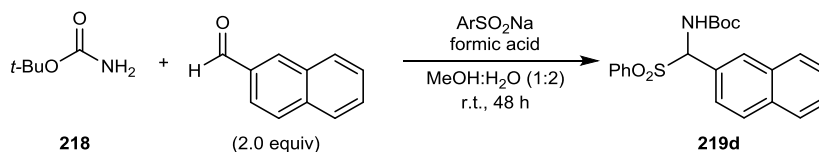
= 7.4 Hz, ArH), 7.60-7.50 (2H, m, ArH), 7.48-7.31 (4H, m, ArH), 5.92 (1H, d, J = 10.6 Hz, NH), 5.81 (1H, d, J = 10.6 Hz, CH), 1.26 (9H, s, C(CH₃)₃); HRMS (ESI) Exact mass calcd for C₁₈H₂₀ClNO₄Na [M+Na]⁺: 404.0703, found: 404.0694. ¹H NMR and ¹³C NMR data were consistent with those reported previously.^{10e}

***tert*-Butyl *N*-[(benzenesulfonyl)(4-methylphenyl)methyl]carbamate (**219c**)**



4-Methylbenzaldehyde (1.8 mL, 15.0 mmol) was suspended in 2:1:0.7 H₂O/MeOH/HCO₂H (40 mL). Sodium benzenesulfinate (3.28 g, 20.0 mmol) and *tert*-butyl carbamate (**218**) (1.17 g, 10.0 mmol) were added sequentially and the reaction mixture was stirred for 4 days. The solids were collected by filtration and triturated with H₂O and then 5:3 hexane/toluene to yield the title compound as a white solid (3.28 g, 91%). ¹H NMR (500 MHz, CDCl₃) δ 7.93 (2H, d, J = 7.5 Hz, ArH), 7.65 (1H, t, J = 7.5 Hz, ArH), 7.55 (2H, t, J = 7.5 Hz, ArH), 7.34 (2H, d, J = 8.1 Hz, ArH), 7.24 (2H, d, J = 8.1 Hz, ArH), 5.89 (1H, d, J = 10.6 Hz, NH), 5.69 (1H, d, J = 10.6 Hz, CH), 2.38 (2H, s, ArCH₃), 1.25 (9H, s, C(CH₃)₃); ¹³C NMR (125.6 MHz, CDCl₃) δ 153.4 (C), 139.9 (C), 137.0 (C), 133.8 (CH), 129.4 (4 \times CH), 129.0 (2 \times CH), 128.8 (2 \times CH), 126.7 (C), 81.0 (C), 73.7 (CH), 27.9 (3 \times CH₃), 21.3 (CH₃). ¹H NMR and ¹³C NMR data were consistent with those reported previously.^{10e}

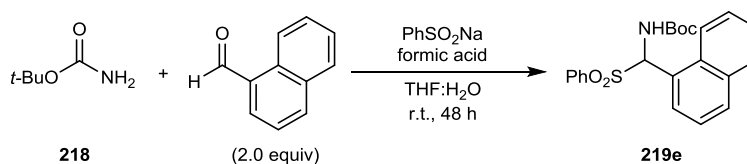
***tert*-Butyl *N*-[(benzenesulfonyl)(naphthalen-2-yl)methyl]carbamate (**219d**)**



2-Naphthaldehyde (2.34 g, 15.0 mmol) was suspended in 2:1:0.7 H₂O/MeOH/HCO₂H (40 mL). Sodium benzenesulfinate (3.28 g, 20.0 mmol) and *tert*-butyl carbamate (**218**) (1.17 g, 10.0 mmol) were added sequentially and the reaction mixture was stirred for 2 days. The solids were collected by filtration and triturated with H₂O and then Et₂O to yield the title compound as a white solid (1.72 g, 43%). -

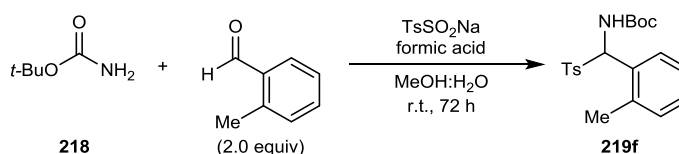
^1H NMR (400 MHz, CDCl_3) δ 8.00-7.86 (6H, m, ArH), 7.68 (1H, t, $J = 7.1$ Hz, ArH), 7.61-7.55 (5H, m, ArH), 6.12 (1H, d, $J = 10.5$ Hz, NH), 5.88 (1H, d, $J = 10.5$ Hz, CH), 1.31 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100.6 MHz, CDCl_3) δ 153.3 (C), 136.9 (C), 134.0 (C), 133.7 (C), 132.9 (C), 129.5 (CH), 129.1 (CH), 129.0 (CH), 128.6 (CH), 128.3 ($2 \times \text{CH}$), 127.7 ($2 \times \text{CH}$), 127.2 (CH), 127.1 (CH), 126.7 (CH), 125.5 (CH), 81.3 (C), 74.1 (CH), 28.0 ($3 \times \text{CH}_3$). ^1H NMR and ^{13}C NMR data were consistent with those reported previously.⁹²

***tert*-Butyl *N*-[(benzenesulfonyl)(naphthalen-1-yl)methyl]carbamate (219e)**



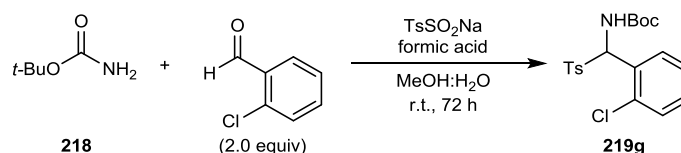
1-Naphthaldehyde (1.35 mL, 10.0 mmol) was suspended in 10:3.5:1.9 H_2O /THF/ HCO_2H (15.4 mL). Sodium benzenesulfinate (1.64 g, 10.0 mmol) and *tert*-butyl carbamate (**218**) (1.17 g, 10.0 mmol) were added sequentially and the reaction mixture was stirred for 2 days. The solids were collected by filtration and triturated with H_2O and then MTBE to yield the title compound as a white solid (1.83 g, 46%). ^1H NMR (400 MHz, CDCl_3) δ 8.13 (1H, d, $J = 8.4$ Hz, ArH), 7.99 (2H, d, $J = 8.2$ Hz, ArH), 7.95 (1H, d, $J = 8.2$ Hz, ArH), 7.89 (1H, d, $J = 7.9$ Hz, ArH), 7.79 (1H, $J = 7.3$ Hz, ArH), 7.67-7.48 (6H, m, ArH), 6.87 (1H, d, $J = 10.5$ Hz, CH), 5.91 (1H, d, $J = 10.5$ Hz, NH), 1.28 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100.6 MHz, CDCl_3) δ 156.3 (C), 137.3 (C), 133.9 (C), 133.6 (C), 131.7 (C), 130.5 ($2 \times \text{CH}$), 129.4 (CH), 129.0 ($2 \times \text{CH}$), 128.9 (CH), 127.2 (CH), 127.0 (CH), 126.5 (CH), 126.2 (CH), 125.1 (CH), 122.8 (CH), 81.2 (C), 69.0 (CH), 28.0 ($3 \times \text{CH}_3$); HRMS (ESI) Exact mass calcd for $\text{C}_{22}\text{H}_{23}\text{NO}_4\text{SNa}$ $[\text{M}+\text{Na}]^+$: 420.1240, found: 420.1226. ^1H NMR and ^{13}C NMR data were consistent with those reported previously.⁷⁷

***tert*-Butyl *N*-[(4-methylbenzenesulfonyl)(2-methylphenyl)methyl]carbamate (218f)**



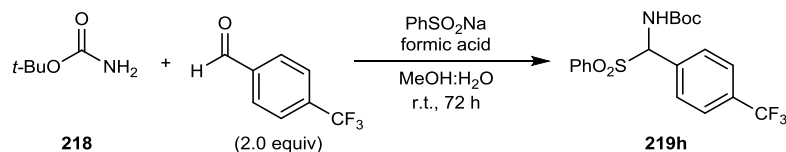
2-Tolualdehyde (1.70 mL, 15.0 mmol) was suspended in 2:1:0.7 H₂O/MeOH/HCO₂H (40 mL). Sodium *p*-toluenesulfinate (3.56 g, 20.0 mmol) and *tert*-butyl carbamate (**218**) (1.17 g, 15.0 mmol) were added sequentially and the reaction mixture was stirred for 3 days. The solids were collected by filtration and triturated with H₂O then 1:5 MTBE/*iso*-hexane to yield the title compound as a white solid (3.23 g, 86%). ¹H NMR (400 MHz, CDCl₃) δ 7.80 (2H, d, *J* = 8.2 Hz, ArH), 7.48-7.41 (1H, m, ArH), 7.36-7.28 (4H, m, ArH), 7.25-7.20 (1H, m, ArH), 6.22 (1H, d, *J* = 10.7 Hz, NH), 5.76 (1H, d, *J* = 10.7 Hz, CH), 2.46 (3H, s, ArCH₃), 2.44 (3H, s, ArCH₃), 1.27 (9H, s, C(CH₃)₃); HRMS (ESI) Exact mass calcd for C₂₀H₂₅NO₄SNa [M+Na]⁺: 398.1397, found: 398.1400. ¹H NMR data was consistent with those reported previously.⁹³

***tert*-Butyl N-[(2-chlorophenyl)(4-methylbenzenesulfonyl)methyl]carbamate (219g)**



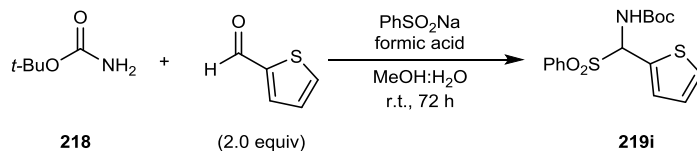
2-Chlorobenzaldehyde (1.70 mL, 15.0 mmol) was suspended in 2:1:0.7 H₂O/MeOH/HCO₂H (40 mL). Sodium *p*-toluenesulfinate (3.56 g, 20.0 mmol) and *tert*-butyl carbamate (**218**) (1.17 g, 15.0 mmol) were added sequentially and the reaction mixture was stirred for 3 days. The solids were collected by filtration and triturated with H₂O and then 1:5 MTBE/*iso*-hexane to yield the title compound as a white solid (2.65 g, 67%). ¹H NMR (400 MHz, CDCl₃) δ 7.81 (2H, d, *J* = 8.0 Hz, ArH), 7.60-7.53 (1H, m, ArH), 7.46-7.40 (1H, m, ArH), 7.39-7.29 (4H, m, ArH), 6.58 (1H, d, *J* = 10.7 Hz, CH), 5.95-5.80 (1H, m, NH), 2.44 (3H, s, ArCH₃), 1.30 (9H, s, C(CH₃)₃); HRMS (ESI) Exact mass calcd for C₁₉H₂₂ClNO₄SNa [M+H]⁺: 418.0850, found: 418.0852. ¹H NMR data was consistent with those reported previously.⁹³

***tert*-Butyl *N*-[(benzenesulfonyl)[4-(trifluoromethyl)phenyl]methyl]carbamate (219h)**



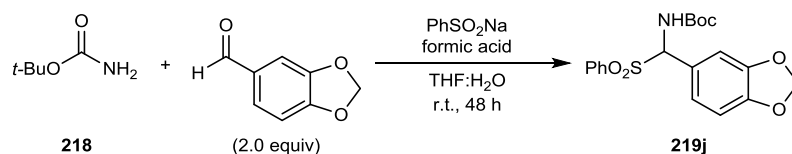
4-(Trifluoromethyl)benzaldehyde (3.10 mL, 22.5 mmol) was suspended in 2:1:0.7 H₂O/MeOH/HCO₂H (40 mL). Sodium benzenesulfinate (4.92 g, 30.0 mmol) and *tert*-butyl carbamate (**218**) (1.76 g, 15.0 mmol) were added sequentially and the reaction mixture was stirred for 3 days. The solids were collected by filtration and triturated with H₂O and then Et₂O to yield the title compound as a white solid (4.00 g, 65%). ¹H NMR (300 MHz, CDCl₃) δ 7.95 (2H, d, *J* = 7.5 Hz, ArH), 7.73-7.64 (3H, m, ArH), 7.64-7.53 (4H, m, ArH), 6.03 (1H, d, *J* = 10.6 Hz, NH), 5.92 (1H, d, *J* = 10.6 Hz, CH), 1.25 (9H, s, C(CH₃)₃); HRMS (ESI) Exact mass calcd for C₁₉H₂₀F₃NO₄SNa [M+Na]⁺: 438.0957, found: 438.0970. ¹H NMR data was consistent with those reported previously.⁹⁴

***tert*-Butyl *N*-[(benzenesulfonyl)(thiophen-2-yl)methyl]carbamate (219i)**



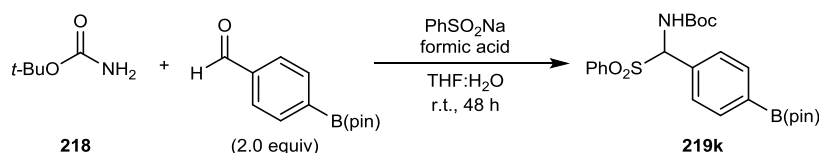
2-Thiophenecarbaldehyde (2.10 mL, 22.5 mmol) was suspended in 2:1:0.7 H₂O/MeOH/HCO₂H (40 mL). Sodium benzenesulfinate (4.92 g, 30.0 mmol) and *tert*-butyl carbamate (**218**) (1.76 g, 15.0 mmol) were added sequentially and the reaction mixture was stirred for 3 days. The solids were collected by filtration and triturated with H₂O and then hexane to yield the title compound as a white solid (2.52 g, 49%). ¹H NMR (400 MHz, CDCl₃) δ 7.95 (2H, d, *J* = 7.4 Hz, ArH), 7.67 (1H, t, *J* = 7.4 Hz, ArH), 7.56 (2H, t, *J* = 7.7 Hz, ArH), 7.44 (1H, dd, *J* = 5.1, 1.2 Hz, thienyl H), 7.29 (1H, m, thienyl H), 7.09 (1H, dd, *J* = 5.1, 1.2 Hz, thienyl H), 6.21 (1H, d, *J* = 10.6 Hz, CH), 5.70 (1H, d, *J* = 10.6 Hz, NH), 1.28 (9H, s, C(CH₃)₃); HRMS (ESI): calcd for [M+H]⁺ C₁₉H₁₆NO₄S₂: 354.0833, found: 354.0855. ¹H NMR data was consistent with those reported previously.⁹²

***tert*-Butyl *N*-[(benzenesulfonyl)(2H-1,3-benzodioxol-5-yl)methyl]carbamate (219j)**



Piperonal (1.50 g, 10.0 mmol) was suspended in 10:3.5:1.9 H₂O/THF/HCO₂H (15.4 mL). Sodium benzenesulfinate (1.64 g, 10.0 mmol) and *tert*-butyl-carbamate (**218**) (1.17 g, 10.0 mmol) were added sequentially and the reaction mixture was stirred for 2 days. The reaction mixture was dissolved in CH₂Cl₂ (50 mL) and H₂O (50 mL). The aqueous layer was extracted with CH₂Cl₂ (2 × 25 mL) then dried (MgSO₄). The crude residue was triturated with 1:5 Et₂O/*iso*-hexane to yield the title compound as a white solid (1.92 g, 49%). ¹H NMR (400 MHz, CDCl₃) δ 7.97-7.92 (2H, m, ArH), 7.67 (1H, t, *J* = 7.4 Hz, ArH), 7.57 (2H, t, *J* = 7.6 Hz, ArH), 6.98 (1H, d, *J* = 1.6 Hz, ArH), 6.93 (1H, dd, *J* = 8.1, 1.6 Hz, ArH), 6.85 (1H, d, *J* = 8.1 Hz, ArH), 6.03 (2H, s, CH₂), 5.84 (1H, d, *J* = 10.6 Hz, CH), 5.65 (1H, d, *J* = 10.6 Hz, NH), 1.27 (9H, s, C(CH₃)₃); HRMS (ESI): calcd for [M+H]⁺ C₁₉H₂₁NO₆S: 392.1168, found: 392.1192. ¹H NMR data was consistent with those reported previously.⁹⁵

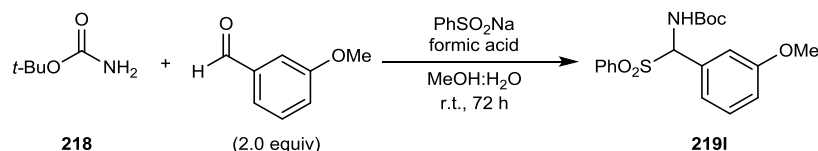
***tert*-Butyl *N*-[(4-methylbenzenesulfonyl)[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methyl]carbamate (219k)**



4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-benzaldehyde (1.44 g, 6.20 mmol) was suspended in 6.2:2.1:1.2 H₂O/THF/HCO₂H (9.5 mL). Sodium benzenesulfinate (1.01 g, 6.20 mmol) and *tert*-butyl-carbamate (**218**) (726 mg, 6.2 mmol) were added sequentially and the reaction mixture was stirred for 2 days. The reaction mixture was dissolved in CH₂Cl₂ (50 mL) and H₂O (50 mL). The aqueous layer was extracted with CH₂Cl₂ (2 × 25 mL) then dried (MgSO₄). The crude residue was triturated with MTBE to yield the title compound as a white solid (1.10 g, 38%). ¹H NMR (400 MHz, CDCl₃) δ 7.99-7.80 (5H, m, ArH), 7.63 (1H, t, *J* = 7.6 Hz, ArH), 7.55-7.50

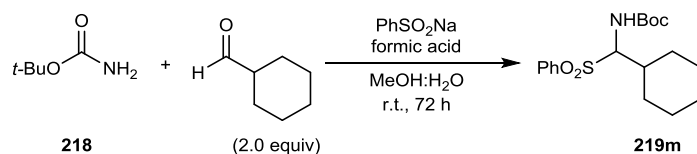
(2H, m, ArH), 7.46-7.41 (2H, m, ArH), 5.94 (1H, d, $J = 10.6$ Hz, NH), 5.87 (1H, d, $J = 10.6$ Hz, CH), 1.34 (12H, s, $2 \times \text{C}(\text{CH}_3)_2$), 1.25 (9H, s, $\text{C}(\text{CH}_3)_3$); HRMS (ESI) Exact mass calcd for $[\text{M}+\text{NH}_4]^+$ $\text{C}_{24}\text{H}_{36}\text{BN}_2\text{O}_6\text{S}$: 491.2387, found: 491.2425. ^1H NMR data was consistent with those reported previously.⁹⁵

***tert*-Butyl *N*-[(benzenesulfonyl)(3-methoxyphenyl)methyl]carbamate (219l)**



m-Anisaldehyde (2.70 mL, 22.2 mmol) was suspended in 2:1:0.7 $\text{H}_2\text{O}/\text{MeOH}/\text{HCO}_2\text{H}$ (40 mL). Sodium benzenesulfinate (4.92 g, 30.0 mmol) and *tert*-butyl carbamate (**218**) (1.76 g, 15.0 mmol) were added sequentially and the reaction mixture was stirred for 3 days. The solids were collected by filtration and triturated with H_2O then 1:1 hexane/ Et_2O to yield the title compound as a white solid (4.90 g, 87%). ^1H NMR (400 MHz, CDCl_3) δ 7.93 (2H, d, $J = 7.6$ Hz, ArH), 7.65 (1H, t, $J = 7.4$ Hz, ArH), 7.58-7.48 (2H, m, ArH), 7.32 (1H, dd, $J = 8.4, 7.8$ Hz, ArH), 7.02 (1H, d, $J = 7.6$ Hz, ArH), 7.00-6.94 (2H, m, ArH), 5.91 (1H, d, $J = 10.8$ Hz, CH), 5.82 (1H, d, $J = 10.8$ Hz, NH), 3.80 (3H, s, OCH_3), 1.26 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100.6 MHz, CDCl_3) δ 159.7 (C), 153.5 (C), 136.9 (C), 133.9 (CH), 131.3 (C), 129.8 ($2 \times \text{CH}$), 129.4 (CH), 129.0 ($2 \times \text{CH}$), 121.12 (CH), 115.6 (CH), 114.4 (CH), 81.2 (C), 73.9 (CH), 55.3 (CH_3), 28.0 ($3 \times \text{CH}_3$); HRMS (ESI) Exact mass calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_5\text{SNa}$ $[\text{M}+\text{Na}]^+$: 400.1189, found: 400.1184. ^1H NMR and ^{13}C NMR data were consistent with those reported previously.^{10e}

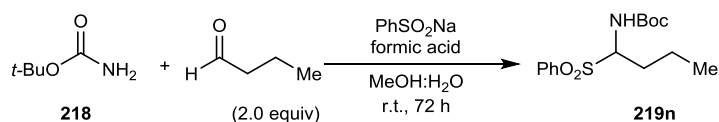
***tert*-Butyl *N*-[(benzenesulfonyl)(cyclohexyl)methyl]carbamate (219m)**



Cyclohexanecarboxyaldehyde (1.80 mL, 14.9 mmol) was suspended in 2:1:0.7 $\text{H}_2\text{O}/\text{MeOH}/\text{HCO}_2\text{H}$ (30 mL). Sodium benzenesulfinate (4.27 g, 26.0 mmol) and *tert*-butyl carbamate (**218**) (1.17 g, 10.0 mmol) were added sequentially and the reaction mixture was stirred for 3 days. The solids were collected by filtration and

trituated with H₂O and then hexane to yield the title compound as a white solid (3.48 g, 95%). ¹H NMR (400 MHz, CDCl₃) δ 7.93-7.85 (2H, m, ArH), 7.71-7.45 (3H, m, ArH), 5.22 (1H, d, *J* = 11.2 Hz, NH), 4.71 (1H, dd, *J* = 11.2, 3.7 Hz, CH), 2.51-2.39 (1H, m, CH), 2.13 (1H, d, *J* = 12.5 Hz, CH), 1.85-1.71 (3H, m, CH), 1.67 (1H, d, *J* = 12.9 Hz, CH), 1.45-1.07 (14H, m, CH); ¹³C NMR (100.6 MHz, CDCl₃) δ 153.9 (C), 138.0 (C), 133.6 (CH), 128.91 (2 × CH), 128.87 (2 × CH), 80.6 (C), 74.3 (CH), 36.2 (CH), 30.5 (CH₂), 27.9 (3 × CH₃) 27.3 (CH₂), 25.9 (CH₂), 25.8 (CH₂), 25.6 (CH₂); HRMS (ESI) Exact mass calcd for C₁₈H₂₇NNaO₄S [M+Na]⁺: 376.1553, found: 376.1532. ¹H NMR and ¹³C NMR data were consistent with those reported previously.⁹⁴

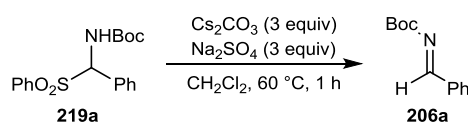
***tert*-Butyl *N*-[1-(benzenesulfonyl)butyl]carbamate (219n)**



Butylaldehyde (1.35 mL, 15.0 mmol) was suspended in 2:1:0.7 H₂O/MeOH/HCO₂H (30 mL). Sodium benzenesulfinate (4.27 g, 26.0 mmol) and *tert*-butyl carbamate (**225**) (1.17 g, 10.0 mmol) were added sequentially. The reaction mixture was stirred for 3 days, the solids collected by filtration and trituated with H₂O and then hexane to yield the title compound as a white solid (2.60 g, 83%). IR (CHCl₃) 3287 (NH), 2960, 1691 (C=O), 1528, 1311, 1146, 1084 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.92 (2H, d, *J* = 7.2 Hz, ArH), 7.66-7.59 (1H, m, ArH), 7.59-7.51 (2H, m, ArH), 4.98 (1H, d, *J* = 10.8 Hz, NH), 4.86 (1H, td, *J* = 10.8, 3.3 Hz, CH), 2.28-2.16 (1H, m, CH_XCH_Y), 1.81-1.65 (1H, m, CH_XH_Y), 1.49-1.36 (1H, m, CH₂), 1.21 (9H, s, C(CH₃)₃), 0.98 (3H, t, *J* = 7.4 Hz, CH₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 153.8 (C), 137.0 (C), 133.8 (CH), 129.3 (2 × CH), 129.0 (2 × CH), 80.8 (C), 70.6 (CH), 28.3 (3 × CH₃), 28.2 (CH₂), 27.7 (CH₂), 13.5 (CH₃); HRMS (ESI) Exact mass calcd for C₁₅H₂₃NNaO₄S [M+Na]⁺: 336.1240, found: 336.1228.

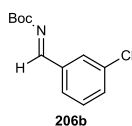
4.2.3.2 *N*-Boc Imines

Representative Procedure: *tert*-Butyl *N*-[(1*E*)-phenylmethylidene]carbamate (**206a**)



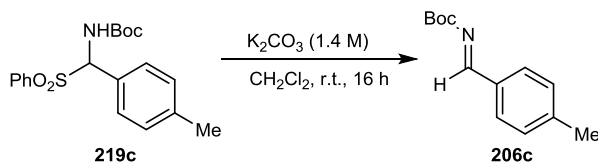
A suspension of flame dried Cs_2CO_3 (3.90 g, 12.0 mmol) and Na_2SO_4 (1.70 g, 12.0 mmol) in a solution of *sulfonylcarbamate* **219a** (1.39 g, 4.00 mmol) in anhydrous alcohol-free CH_2Cl_2 (80 mL) was heated at reflux. After 2 h, the reaction was cooled to room temperature, diluted with petroleum ether, stirred for 10 min and filtered. The filtrate was concentrated *in vacuo* to give *imine* **206a** (814 mg, 99%) as colourless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.88 (1H, s, CH), 7.93 (2H, d, $J = 6.1$ Hz, ArH), 7.60-7.55 (1H, m, ArH), 7.48 (2H, t, $J = 7.5$ Hz, ArH), 1.60 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (126 MHz, CDCl_3) δ 169.7 (CH), 162.6 (C), 134.1 (C), 133.5 (CH), 130.2 ($2 \times \text{CH}$), 128.8 ($2 \times \text{CH}$), 82.3 (C), 27.9 ($3 \times \text{CH}_3$). ^1H NMR and ^{13}C NMR data were consistent with those reported previously.⁹²

***tert*-Butyl *N*-[(1*E*)-(3-chlorophenyl)methylidene]carbamate (**206b**).**



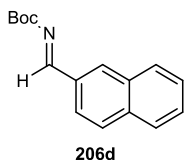
The title compound was prepared according to the Representative Procedure from *sulfonylcarbamate* **219b** (760 mg, 2.00 mmol) to give *imine* **206b** (468 mg, 97%) as a colourless oil. ^1H NMR (300 MHz, CDCl_3) δ 8.80 (1H, s, CH), 7.96 (1H, t, $J = 1.8$ Hz, ArH), 7.76 (1H, dt, $J = 7.6, 1.3$ Hz, ArH), 7.53 (1H ddd, $J = 8.0, 2.1, 1.2$ Hz, ArH), 7.42 (1H, t, $J = 7.8$ Hz, ArH), 1.60 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (100.6 MHz, CDCl_3) δ 167.9 (CH), 162.1 (C), 135.8 (C), 135.2 (C), 133.3 (CH), 130.1 (CH), 129.3 (CH), 128.5 (CH), 82.6 (C), 27.9 ($3 \times \text{CH}_3$). ^1H NMR data was consistent with those reported previously.⁹⁶

***tert*-Butyl *N*-[(1*E*)-(4-methylphenyl)methylidene]carbamate (**206c**)**



Sulfonylcarbamate **219c** (1.45 g, 4.00 mmol) was dissolved in CH_2Cl_2 (64 mL) and K_2CO_3 (1.4 M solution) and stirred for 16 h. The aqueous layer was extracted with CH_2Cl_2 (2×50 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give *imine* **206c** (870 mg, 99%) as a pale yellow oil. ^1H

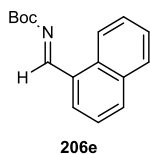
NMR (400 MHz, CDCl₃) δ 8.88 (1H, s, CH), 7.82 (2H, d, J = 8.0 Hz, ArH), 7.28 (2H, d, J = 8.0 Hz, ArH), 2.42 (3H, s, ArCH₃), 1.59 (9H, s, C(CH₃)₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 168.4 (CH), 162.5 (C), 143.7 (C), 132.1 (C), 130.2 (2 \times CH), 129.7 (2 \times CH), 81.0 (C), 27.9 (3 \times CH₃), 21.4 (CH₃). ¹H NMR and ¹³C NMR data were consistent with those reported previously.⁹²



tert-Butyl N-[(1E)-naphthalen-2-ylmethylidene]carbamate

(206d). The title compound was prepared according to the Representative Procedure from *sulfonylcarbamate 219d* (795 mg,

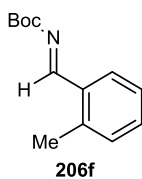
2.00 mmol) to give *imine 206d* (418 mg, 82%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 9.06 (1H, s, CH), 8.30 (1H, s, ArH), 8.10 (1H, dd, J = 8.6, 1.6 Hz, ArH), 8.00-7.85 (3H, m, ArH), 7.68-7.52 (2H, m, ArH), 1.63 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 169.9 (CH), 162.7 (C), 136.0 (C), 134.2 (CH), 132.8 (C), 129.2 (CH), 128.9 (CH), 128.6 (CH), 128.0 (CH), 126.9 (CH), 124.0 (CH), 82.3 (C), 28.0 (3 \times CH₃). ¹H NMR and ¹³C NMR data were consistent with those reported previously.⁹²



tert-Butyl N-[(1E)-naphthalen-1-ylmethylidene]carbamate (206e).

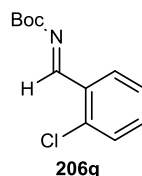
The title compound was prepared according to the Representative Procedure from *sulfonylcarbamate 219e* (795 mg, 2.00 mmol) to give

imine 206e (498 mg, 97%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 9.55 (1H, s, CH), 8.93 (1H, d, J = 8.6 Hz, ArH), 8.19 (1H, dd, J = 7.2, 1.1 Hz, ArH), 8.05 (1H, d, J = 8.2 Hz, ArH), 7.93-7.89 (1H, m, ArH), 7.66 (1H, ddd, J = 8.5, 6.9, 1.4 Hz, ArH), 7.62-7.50 (2H, m, ArH), 1.64 (9H, s, C(CH₃)₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 168.9 (CH), 162.8 (C), 134.3 (C), 133.7 (C), 131.92 (CH), 131.86 (CH), 129.3 (C), 128.8 (CH), 128.0 (CH), 126.5 (CH), 125.0 (CH), 123.9 (CH), 82.2 (C), 27.9 (3 \times CH₃). ¹H NMR and ¹³C NMR data were consistent with those reported previously.⁷⁷



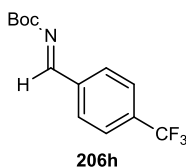
***tert*-Butyl *N*-[(1*E*)-(2-methylphenyl)methylidene]carbamate (**206f**).**

The title compound was prepared according to the Representative Procedure from *sulfonylcarbamate* **219f** (1.50 g, 4.00 mmol) to give *imine* **206f** (850 mg, 97%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 9.22 (1H, s, CH), 8.08 (1H, dd, *J* = 7.8, 1.1 Hz, ArH), 7.42 (1H, td, *J* = 7.5, 1.4 Hz, ArH), 7.27 (1H, t, *J* = 7.6 Hz, ArH), 7.23 (1H, d, *J* = 7.6 Hz, ArH), 2.64 (3H, s, ArCH₃), 1.60 (9H, s, C(CH₃)₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 168.0 (CH), 163.0 (C), 140.8 (C), 133.2 (CH), 131.9 (CH), 131.1 (C), 128.7 (CH), 126.3 (CH), 82.1 (C), 27.9 (3 × CH₃), 19.2 (CH₃). ¹H NMR and ¹³C NMR data were consistent with those reported previously.⁹⁴



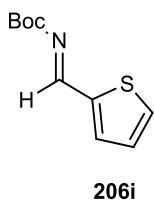
***tert*-Butyl *N*-[(1*E*)-(2-chlorophenyl)methylidene]carbamate (**206g**).**

The title compound was prepared according to the Representative Procedure from *sulfonylcarbamate* **219g** (792 mg, 2.00 mmol) to give *imine* **206g** (462 mg, 96%) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 9.27 (1H, s, CH), 8.18 (1H, dd, *J* = 7.9, 1.6 Hz, ArH), 7.49-7.40 (2H, m, ArH), 7.35-7.30 (1H, m, ArH), 1.59 (9H, s, C(CH₃)₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 165.7 (CH), 162.4 (C), 137.8 (C), 134.2 (CH), 131.3 (C), 130.2 (CH), 129.1 (CH), 127.2 (CH), 82.6 (C), 27.9 (3 × CH₃). ¹H NMR and ¹³C NMR data were consistent with those reported previously.⁹⁷



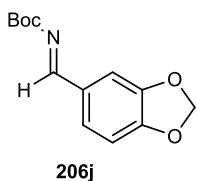
***tert*-Butyl *N*-[(1*E*)-[4-(trifluoromethyl)phenyl]methylidene]carbamate (**206h**).**

The title compound was prepared according to the Representative Procedure from *sulfonylcarbamate* **219h** (831 mg, 2.00 mmol) to give *imine* **206h** (530 mg, 97%). ¹H NMR (400 MHz, CDCl₃) δ 8.86 (1H, s, CH), 7.80 (2H, d, *J* = 8.0 Hz, ArH), 7.27 (2H, d, *J* = 8.0 Hz, ArH), 1.59 (9H, s, C(CH₃)₃). ¹H NMR data were consistent with those reported previously.⁹⁴



***tert*-Butyl *N*-[(1*E*)-thiophen-2-ylmethylidene]carbamate (**206i**).**

The title compound was prepared according to the Representative Procedure from *sulfonylcarbamate* **219i** (353 mg, 1.00 mmol) to give *imine* **206i** (209 mg, 98%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 9.07 (1H, s, CHN), 7.68-7.63 (2H, m, thienylH), 7.1-7.14 (1H, m, thienylH), 1.57 (9H, s, C(CH₃)₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 163.4 (CH), 162.1 (C), 140.2 (C), 137.0 (CH), 134.1 (CH), 128.3 (CH), 82.0 (C), 27.8 (3 × CH₃). ¹H NMR and ¹³C NMR data were consistent with those reported previously.⁹²

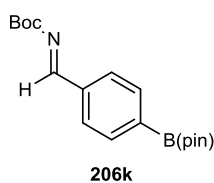


***tert*-Butyl**

***N*-[(1*E*)-2*H*-1,3-benzodioxol-5-**

ylmethylidene]carbamate (206j**).** The title compound was

prepared according to the Representative Procedure from *sulfonylcarbamate* **219j** (784 mg, 2.00 mmol) give *imine* **206j** (475 mg, 97%) as a white solid. m.p 53-55 °C (not recrystallized); IR (CHCl₃) 3010, 1707 (C=O), 1621, 1597, 1505, 1492, 1452, 1243, 1154, 1103 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.82 (1H, s, CH), 7.53 (1H, d, *J* = 1.2 Hz, ArH), 7.36 (1H, dd, *J* = 8.0, 1.2 Hz, ArH), 6.89 (1H, d, *J* = 8.0 Hz, ArH), 6.07 (2H, s, CH₂), 1.57 (9H, s, C(CH₃)₃); ¹³C NMR (100.6 MHz, CDCl₃) δ 169.5 (CH), 162.7 (C), 152.6 (C), 148.6 (C), 128.9 (CH), 128.8 (C), 108.3 (CH), 107.6 (CH), 102.0 (CH₂), 82.0 (C), 27.9 (3 × CH₃); HRMS (ESI) Exact mass calcd for C₁₃H₁₅NO₄Na [M+Na]⁺: 272.0893, found: 272.0896.



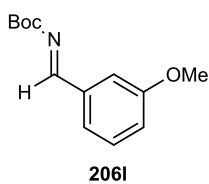
***tert*-Butyl**

***N*-[(1*E*)-4-(tetramethyl-1,3,2-dioxaborolan-2-**

yl)phenyl]methylidene]carbamate (206k**).** The title compound

was prepared according to the Representative Procedure from *sulfonylcarbamate* **219k** (947 mg, 2.00 mmol) to give *imine* **206k** (601 mg, 91%) as a white solid. m.p. 103-105 °C (not recrystallized); IR (CHCl₃) 2984, 1711 (C=O), 1623, 1395, 1360, 1272, 1144, 1088, 856 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.88 (1H, s, CH), 7.91 (4H, s, ArH), 1.60 (9H, s, C(CH₃)₃), 1.37 (12H, s, 2 × C(CH₃)₂); ¹³C NMR (100.6 MHz, CDCl₃) δ 169.7 (CH), 162.6 (C), 136.2 (C), 135.1 (2 × CH), 129.2 (2 × CH), 84.2 (2 × C), 82.4 (C), 27.9 (3 × CH₃), 24.9 (4 × CH₃), the carbon next to boron was not observed due to quadrupolar

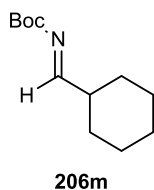
relaxation effects of ^{11}B ; HRMS (ESI) Exact mass calcd for $\text{C}_{18}\text{H}_{26}\text{BNO}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 354.1850, found: 354.1847.



***tert*-Butyl *N*-[(1*E*)-(3-methoxyphenyl)methylidene]carbamate (206l).**

The title compound was prepared according to the Representative Procedure from *sulfonylcarbamate* **219l** (755 mg, 2.00 mmol) to give *imine* **206l** (464 mg, 98%) as a pale yellow oil. -

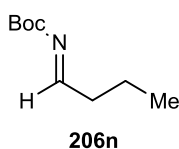
^1H NMR (400 MHz, CDCl_3) δ 8.82 (1H, s, CH), 7.49 (1H, dd, $J = 2.4, 1.3$ Hz, ArH), 7.45-7.33 (2H, m, ArH), 7.10 (1H, ddd, $J = 8.0, 2.7, 1.2$ Hz, ArH), 3.84 (3H, s, OCH_3), 1.59 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (400 MHz, CDCl_3) δ 169.5 (CH), 162.5 (C), 159.9 (C), 135.4 (C), 129.8 (CH), 124.1 (CH), 120.7 (CH), 112.3 (CH), 82.3 (C), 55.4 (CH_3), 28.2 ($3 \times \text{CH}_3$). ^1H NMR and ^{13}C NMR data were consistent with those reported previously.⁹⁸



***tert*-Butyl *N*-[(1*E*)-cyclohexylmethylidene]carbamate (206m).**

The title compound was prepared according to the Representative Procedure from *sulfonylcarbamate* **219m** (707 mg, 2.00 mmol) to give *imine* **206m** (415 mg, 98%) as a colourless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.17 (1H, br, s, CHN), 2.35-2.25 (1H, m, CH), 1.95-1.85

(2H, m, CH_2), 1.84-1.75 (2H, m, CH_2), 1.73-1.65 (1H, m, $\text{CH}_\text{X}\text{H}_\text{Y}$), 1.53 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.38-1.30 (5H, m, $2 \times \text{CH}_2$, $\text{CH}_\text{X}\text{H}_\text{Y}$); ^{13}C NMR (100.6 MHz, CDCl_3) δ 178.1 (CH), 162.3 (C), 81.7 (C), 43.4 (CH), 29.5 (CH_2), 28.4 ($2 \times \text{CH}_2$), 27.7 ($3 \times \text{CH}_3$), 25.7 (CH_2), 25.1 (CH_2). ^1H NMR and ^{13}C NMR data were consistent with those reported previously.⁹⁴



***tert*-Butyl *N*-[(1*E*)-butylidene]carbamate (206n)**

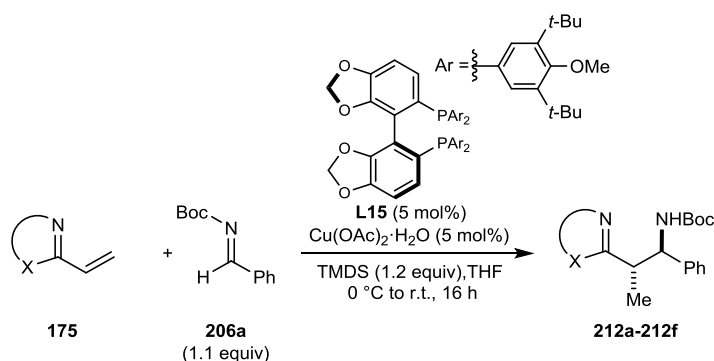
The title compound was prepared according to the Representative Procedure from *sulfonylcarbamate* **219n** (1.17 g, 3.70 mmol) to give *imine* **206n** (340 mg, 99%) as a pale yellow oil. IR (film) 2966, 2937,

2876, 1720.7 ($\text{C}=\text{O}$), 1367, 1251, 1158 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.33 (1H, br, s, CH), 2.46-2.35 (2H, m, CHCH_2), 1.73-1.62 (2H, m, CH_2CH_3), 1.56 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.02 (3H, t, $J = 7.4$ Hz, CH_2CH_3); ^{13}C NMR (400 MHz, CDCl_3) δ 175.5

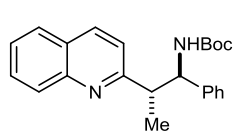
(CH), 167.8 (C), 82.1 (C), 28.4 (CH₂), 28.3 (CH₂), 27.9 (3 × CH₃), 13.7 (CH₃); HRMS (ESI) Exact mass calculated for C₉H₁₇NNaO₂ [M+Na]⁺: 194.1151, found: 194.1161.

4.2.4 Enantioselective Copper-Catalysed Reductive Coupling Reactions

General Procedure A: Reductive Coupling of Vinylazaarenes with Imine **215a** Using Ligand **L15**



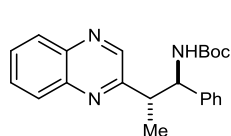
A solution of the appropriate vinylazaarene (0.30 mmol), Cu(OAc)₂·H₂O (3.0 mg, 0.01 mmol), (*S*)-DTBM-SEGPHOS[®] (**L15**) (17.7 mg, 0.015 mmol), and imine **215a** (68 mg, 0.33 mmol) in THF (1.5 mL) was stirred at 0 °C for 15 min. TMSD (64 μL, 0.36 mmol) was then added dropwise over 1 min. The mixture was stirred at 0 °C for 1 h, then at room temperature for 15 h. The reaction was quenched carefully with SiO₂, and the resulting suspension was stirred for 15 min before being filtered through a short plug of SiO₂, using EtOAc as eluent and concentrated *in vacuo*. Purification of the residue by flash column chromatography gave the reductive coupling product.



tert-Butyl N-[(1*R*,2*S*)-1-phenyl-2-(quinolin-2-yl)propyl]carbamate (212a**).** The title compound was prepared according to General Procedure A from 2-vinylquinoline (**175b**)

(47 mg, 0.30 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a white solid (68 mg, 63%). R_f 0.31 (20% EtOAc/petroleum ether); m.p. 128-

131 °C (EtOAc/petroleum ether); $[\alpha]_{\text{D}}^{24} +98.6$ (*c* 1.10, CHCl₃); IR (film) 2970, 2934, 1709 (C=O), 1503, 1390, 1289, 827, 756, 700 cm⁻¹; ¹H NMR (500 MHz, (CD₃)₂CO) δ 8.14 (1H, d, *J* = 8.4 Hz, ArH), 8.05 (1H, d, *J* = 8.3 Hz, ArH), 7.88 (1H, d, *J* = 8.0 Hz, ArH), 7.75 (1H, ddd, *J* = 8.4, 6.9, 1.4 Hz, ArH), 7.57-7.51 (1H, m, ArH), 7.33 (2H, d, *J* = 7.3 Hz, ArH), 7.24 (3H, t, *J* = 8.0 Hz, ArH), 7.16 (2H, t, *J* = 7.0 Hz, ArH and NH), 5.09 (1H, t, *J* = 7.7 Hz, CHN), 3.63-3.54 (1H, m, CHCH₃), 1.35 (3H, d, *J* = 6.9 Hz, CHCH₃), 1.27 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, (CD₃)₂CO) δ 165.1 (C), 156.0 (C), 148.5 (C), 144.1 (C), 137.0 (CH), 130.2 (CH), 129.7 (CH), 128.9 (2 × CH), 128.6 (CH), 128.0 (C), 127.7 (2 × CH), 127.5 (CH), 126.8 (CH), 122.8 (CH), 78.5 (C), 60.2 (CH), 48.1 (CH), 28.5 (3 × CH₃), 19.6 (CH₃); HRMS (ESI) Exact mass calcd for C₂₃H₂₇N₂O₂ [M+H]⁺: 363.2067, found: 363.2067. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); *t*_r (major) = 4.6 min, *t*_r (minor) = 5.9 min; 85% ee.



tert-Butyl

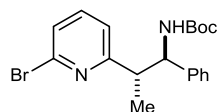
***N*-[(1*R*,2*S*)-1-phenyl-2-(quinoxalin-2-**

yl)propyl]carbamate (212b). The title compound was prepared

according to General Procedure A from 2-vinylquinoxaline

(**175d**) (47 mg, 0.30 mmol) and purified by column chromatography (10% EtOAc/hexane) to give a white solid (75 mg, 69%). *R*_f 0.43 (30% EtOAc/petroleum ether); m.p. 160-162 °C (EtOAc/petroleum ether); $[\alpha]_{\text{D}}^{24} +118.6$ (*c* 1.05, CHCl₃); IR (film) 2970, 2939, 1697 (C=O), 1493, 1454, 1365, 1249, 1168, 760, 700 cm⁻¹; ¹H NMR (500 MHz, (CD₃)₂CO) δ 8.76 (1H, s, ArH), 8.09 (1H, d, *J* = 8.1 Hz, ArH), 8.04 (1H, d, *J* = 7.9 Hz, ArH), 7.83 (1H, t, *J* = 7.7 Hz, ArH), 7.79 (1H, t, *J* = 7.1 Hz, ArH), 7.45 (2H, d, *J* = 7.5 Hz, ArH), 7.33 (2H, t, *J* = 7.5 Hz, ArH), 7.25 (1H, t, *J* = 7.3 Hz, ArH), 6.74 (1H, d, *J* = 8.0 Hz, NH), 5.10 (1H, t, *J* = 8.9 Hz, CHN), 3.79-3.66 (1H, m, CHCH₃), 1.31 (3H, d, *J* = 6.9 Hz, CHCH₃), 1.15 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, (CD₃)₂CO) δ 160.0 (C), 155.7 (C), 147.3 (CH), 143.4 (C), 142.8 (C), 142.5 (C), 130.7 (CH), 130.04 (CH), 129.99 (CH), 129.89 (2 × CH), 129.2 (2 × CH), 128.02 (CH), 127.96 (CH), 78.7 (C), 60.3 (CH), 46.1 (CH), 28.4 (3 × CH₃), 18.6 (CH₃); HRMS (ESI) Exact mass calcd for C₂₂H₂₆N₃O₂ [M+H]⁺: 364.2020, found: 364.2021. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H

column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r (minor) = 11.3 min, t_r (major) = 14.6 min; 92% ee.



***tert*-Butyl**

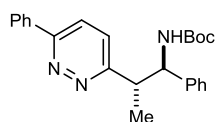
***N*-[2-(6-bromopyridin-2-yl)-1-**

phenylpropyl]carbamate (212c). The title compound was

prepared according to General Procedure A from 6-bromo-2-vinylpyridine (**175p**) (55 mg, 0.30 mmol) and purified by column chromatography (10% EtOAc/*iso*-hexane) to give a 4.3:1 mixture of diastereomers as a white solid (80 mg, 68%). R_f 0.24 (20% EtOAc/petroleum ether); $[\alpha]_D^{22} +121.2$ (c 0.66, CHCl₃); IR (CHCl₃) 3009, 2934, 1709 (C=O), 1584, 1499, 1456, 1435, 1367, 1163, 842 cm⁻¹; Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (99:1 *iso*-hexane:EtOH, 0.3 mL/min, 254 nm, 25 °C); major diastereomer: t_r (major) = 30.2, t_r (minor) = 34.5 min, 80% ee; minor diastereomer: t_r (major) = 46.3, t_r (minor) = 55.0 min, 20% ee.

Major diastereomer: ¹H NMR (400 MHz, (CD₃)₂CO) δ 7.59 (1H, t, J = 7.7 Hz, ArH), 7.41 (1H, d, J = 2.4 Hz, ArH), 7.37 (2H, d, J = 7.2 Hz, ArH), 7.31 (2H, d, J = 7.6 Hz, ArH), 7.23 (2H, d, J = 6.5 Hz, ArH), 6.61 (1H, d, J = 7.8 Hz, NH), 4.92 (1H, t, J = 7.8 Hz, CHN), 3.37-3.30 (1H, m, CHCH₃), 1.27 (9H, s, C(CH₃)₃), 1.13 (3H, d, J = 6.8 Hz, CHCH₃); ¹³C NMR (125.8 MHz, (CD₃)₂CO) δ 166.3 (C), 155.7 (C), 143.6 (C), 141.8 (C), 140.1 (CH), 129.0 (2 \times CH), 128.0 (2 \times CH), 127.8 (CH), 126.7 (CH), 123.2 (CH), 78.6 (C), 60.1 (CH), 47.6 (CH), 28.5 (3 \times CH₃), 19.1 (CH₃).

Diagnostic peaks for minor diastereomer: ¹H NMR (400 MHz, (CD₃)₂CO) δ 8.05 (1H, d, J = 7.3 Hz, ArH), 7.52 (1H, t, J = 7.6 Hz, ArH), 7.46-7.40 (1H, m, ArH), 7.34-7.28 (1H, t, J = 7.6 Hz, ArH), 7.17 (2H, t, J = 7.5 Hz, ArH), 7.10 (1H, d, J = 7.1 Hz, ArH), 7.01 (1H, d, J = 7.5 Hz, ArH), 5.05 (1H, t, J = 9.3 Hz, CHN), 3.45-3.42 (1H, m, CHCH₃), 1.38-1.33 (12H, m, CHCH₃ and C(CH₃)₃); ¹³C NMR (125.8 MHz, (CD₃)₂CO) δ 165.9 (C), 156.1 (C), 143.4 (C), 141.7 (C), 139.9 (CH), 128.7 (2 \times CH), 128.1 (2 \times CH), 127.5 (CH), 126.5 (CH), 123.1 (CH), 78.7 (C), 60.0 (CH), 48.1 (CH), 28.6 (3 \times CH₃), 17.5 (CH₃); HRMS (ESI) Exact mass calcd for C₁₉H₂₄BrN₂O₂ [M+H]⁺: 391.1016, found: 391.1018.



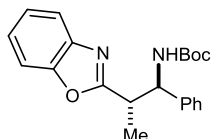
***tert*-Butyl**

***N*-[(1*R*,2*S*)-1-phenyl-2-(6-phenylpyridazin-3-**

yl)propyl]carbamate (212d). The title compound was prepared

according to General Procedure A from 3-phenyl-6-

vinylpyridazine (**175o**) (55 mg, 0.30 mmol) and purified by column chromatography (0.5% Et₃N in 25% EtOAc/hexane) to give a white solid (68 mg, 58%). *R*_f 0.14 (20% EtOAc/petroleum ether); m.p. 181-182 °C (EtOAc/petroleum ether); [α]_D²⁴ +68.0 (*c* 1.00, CHCl₃); IR (film) 2976, 1690 (C=O), 1504, 1497, 1454, 1426, 1365, 1170, 753, 699 cm⁻¹; ¹H NMR (400 MHz, (CD₃)₂CO) δ 8.20-8.14 (2H, m, ArH), 8.01 (1H, d, *J* = 8.8 Hz, ArH), 7.58-7.48 (4H, m, ArH), 7.44-7.40 (2H, m, ArH), 7.32 (2H, t, *J* = 7.5 Hz, ArH), 7.23 (1H, t, *J* = 7.2 Hz, ArH), 6.81 (1H, d, *J* = 8.6 Hz, NH), 5.06 (1H, t, *J* = 8.7 Hz, CHN), 3.71-3.56 (1H, m, CHCH₃), 1.32 (3H, d, *J* = 6.9 Hz, CHCH₃), 1.26 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, (CD₃)₂CO) δ 165.0 (C), 158.3 (C), 155.9 (C), 143.5 (C), 137.6 (C), 130.6 (CH), 129.8 (2 \times CH), 129.1 (2 \times CH), 127.93 (2 \times CH), 127.90 (CH), 127.86 (2 \times CH), 127.7 (CH), 124.6 (CH), 78.8 (C), 60.1 (CH), 46.6 (CH), 28.5 (3 \times CH₃), 19.2 (CH₃); HRMS (ESI) Exact mass calcd for C₂₄H₂₈N₃O₂ [M+H]⁺: 390.2176, found: 390.2176. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); *t*_r (minor) = 10.6 min, *t*_r (major) = 12.0 min; 82% ee.



***tert*-Butyl**

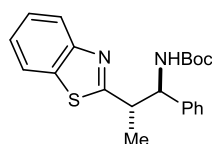
***N*-[(1*S*,2*R*)-2-(1,3-benzoxazol-2-yl)-1-**

phenylpropyl]carbamate (212e). The title compound was

prepared according to General Procedure A from 2-

vinylbenzoxazole (**175l**) (44 mg, 0.30 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a white solid (78 mg, 74%). *R*_f 0.38 (20% EtOAc/petroleum ether); m.p. 93-95 °C (EtOAc/petroleum ether); [α]_D²⁴ +26.6 (*c* 1.02, CHCl₃); IR (film) 2976, 1715 (C=O), 1567, 1497, 1365, 1288, 1171, 1002, 748, 701 cm⁻¹; ¹H NMR (400 MHz, (CD₃)₂CO) δ 7.69-7.65 (1H, m, ArH), 7.57-7.53 (1H, m, ArH), 7.47-7.42 (2H, m, ArH), 7.37-7.29 (4H, m, ArH), 7.25 (1H, t, *J* = 7.2 Hz, ArH), 6.75 (1H, d, *J* = 8.2 Hz, NH), 5.11 (1H, t, *J* = 8.2 Hz, CHN), 3.70-3.59 (1H, m, CHCH₃), 1.33 (3H, d, *J* = 7.7 Hz, CHCH₃), 1.25 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, (CD₃)₂CO) δ 168.9 (C), 155.8 (C), 151.4 (C), 142.3 (C), 142.2 (C), 129.2 (2 \times CH), 128.2 (CH), 127.9 (2 \times CH), 125.5 (CH), 125.0 (CH), 120.4 (CH),

111.3 (CH), 79.0 (C), 59.0 (CH), 41.0 (CH), 28.4 (3 × CH₃), 17.0 (CH₃); HRMS (ESI) Exact mass calcd for C₂₁H₂₅N₂O₃ [M+H]⁺: 353.1860, found: 353.1863. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 °C); t_r (major) = 15.2 min, t_r (minor) = 19.3 min; 75% ee.



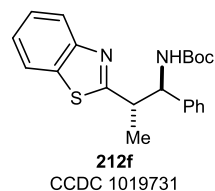
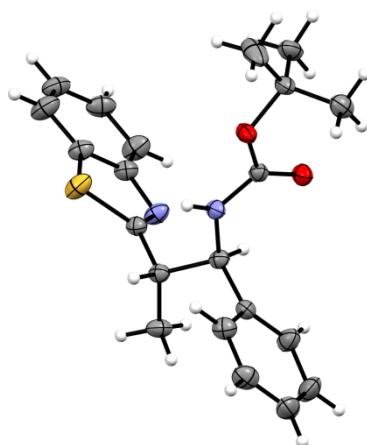
***tert*-Butyl**

***N*-[(1*R*,2*S*)-2-(1,3-benzothiazol-2-yl)-1-**

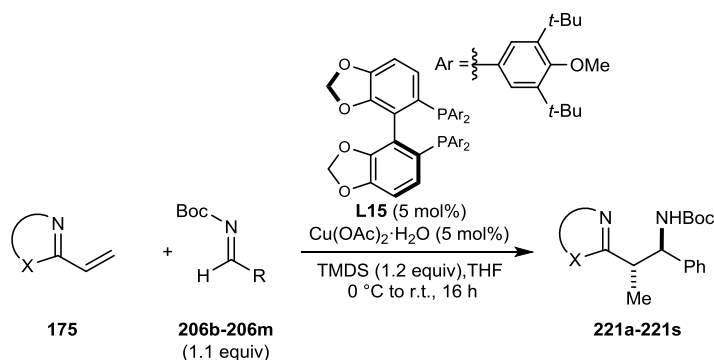
phenylpropyl]carbamate (212f).

The title compound was prepared according to General Procedure A from 2-vinylbenzothiazole (**175k**) (47 mg, 0.30 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a white solid (72 mg, 65%). R_f 0.32 (20% EtOAc/petroleum ether); m.p. 142-145 °C (EtOAc/petroleum ether); [α]_D²⁴ +55.0 (*c* 1.00, CHCl₃); IR (film) 2979, 2928, 1713 (C=O), 1498, 1390, 1365, 1170, 1022, 759, 700 cm⁻¹; ¹H NMR (400 MHz, (CD₃)₂CO) δ 7.98 (2H, t, *J* = 8.9 Hz, ArH), 7.54-7.45 (1H, m, ArH), 7.45-7.35 (3H, m, ArH), 7.30 (2H, t, *J* = 7.4 Hz, ArH), 7.23 (1H, t, *J* = 7.5 Hz, ArH), 6.80 (1H, d, *J* = 7.5 Hz, NH), 5.15-4.90 (1H, m, CHN), 3.88-3.65 (1H, m, CHCH₃), 1.37 (3H, d, *J* = 6.8 Hz, CHCH₃), 1.28 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, (CD₃)₂CO) δ 174.7 (C), 155.9 (C), 154.1 (C), 142.9 (C), 135.6 (C), 129.1 (2 × CH), 128.0 (CH), 127.8 (2 × CH), 126.8 (CH), 125.7 (CH), 123.4 (CH), 122.6 (CH), 78.9 (C), 60.3 (CH), 45.1 (CH), 28.5 (3 × CH₃), 19.5 (CH₃); HRMS (ESI) Exact mass calcd for C₂₁H₂₅N₂O₂S [M+H]⁺: 369.1631, found: 369.1634. Enantiomeric excess was determined by HPLC with a Chiralpak IC column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 280 nm, 25 °C); t_r (major) = 18.9 min, t_r (minor) = 27.9 min; 88% ee.

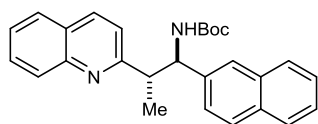
Slow diffusion of hexane into a solution of **212f** in EtOAc provided single crystals that were suitable for X-ray crystallography:



General Procedure B: Reductive Coupling of Vinylazaarenes with Various *N*-Boc Imines Using Ligand **L15**

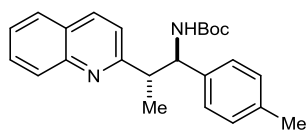


A solution of the appropriate vinylazaarene (0.30 mmol), $\text{Cu}(\text{OAc})_2\cdot\text{H}_2\text{O}$ (3.0 mg, 0.015 mmol), (*S*)-DTBM-SEGPHOS® (**L15**) (17.7 mg, 0.015 mmol), and the appropriate imine (0.33 mmol) in THF (1.5 mL) was stirred at 0 °C for 15 min. TMSD (64 μL , 0.36 mmol) was then added dropwise over 1 min. The mixture was stirred at 0 °C for 1 h, then at room temperature for 16 h. The reaction was quenched carefully with SiO_2 , and the resulting suspension was stirred for 15 min before being filtered through a short plug of SiO_2 , using EtOAc as eluent and concentrated *in vacuo*. Purification of the residue by column chromatography gave the reductive coupling product.



tert-Butyl N-[(1*R*,2*S*)-1-(naphthalen-2-yl)-2-(quinolin-2-yl)propyl]carbamate (221a**)**. The title compound was prepared according to General Procedure B from 2-vinylquinoline (**175b**) (47 mg, 0.30 mmol) and *N*-Boc imine **206d** (84 mg, 0.33

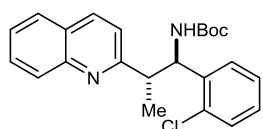
mmol) and purified by column chromatography (5-10% EtOAc/*iso*-hexane) to give a white solid (73 mg, 58%). R_f 0.33 (20% EtOAc/petroleum ether); m.p. 156-158 °C (EtOAc/petroleum ether); $[\alpha]_D^{24} +144.8$ (c 1.02, CHCl₃); IR (film) 2973, 2928, 1707 (C=O), 1503, 1365, 1169, 1048, 858, 818, 755 cm⁻¹; ¹H NMR (400 MHz, (CD₃)₂CO) δ 8.11 (1H, d, J = 8.4 Hz, ArH), 8.08 (1H, d, J = 8.4 Hz, ArH), 7.91-7.72 (6H, m, ArH), 7.58-7.52 (2H, m, ArH), 7.48-7.40 (2H, m, ArH), 7.27 (1H, d, J = 8.4 Hz, ArH), 7.23 (1H, d, J = 7.2 Hz, NH), 5.35-5.11 (1H, m, CHN), 3.79-3.58 (1H, m, CHCH₃), 1.38 (3H, d, J = 7.0 Hz, CHCH₃), 1.27 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, (CD₃)₂CO) δ 165.1 (C), 156.1 (C), 148.5 (C), 141.6 (C), 137.1 (CH), 134.2 (C), 133.6 (C), 130.2 (CH), 129.8 (CH), 128.65 (CH), 128.62 (CH), 128.61 (CH), 128.4 (CH), 128.0 (C), 126.8 (2 \times CH), 126.5 (CH), 126.4 (CH), 126.0 (CH), 122.8 (CH), 78.6 (C), 60.4 (CH), 48.0 (CH), 28.5 (3 \times CH₃), 19.7 (CH₃); HRMS (ESI) Exact mass calcd for C₂₇H₂₉N₂O₂ [M+H]⁺: 413.2224, found: 413.2226. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r (major) = 18.1 min, t_r (minor) = 21.9 min; 86% ee.



***tert*-Butyl *N*-[(1*R*,2*S*)-1-(4-methylphenyl)-2-(quinolin-2-yl)propyl]carbamate (221b).** The title compound was prepared according to General Procedure B from 2-

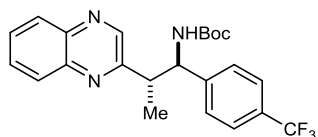
vinylquinoline (**175b**) (47 mg, 0.30 mmol) and *N*-Boc imine **206c** (72 mg, 0.33 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a white solid (68 mg, 61%). R_f 0.60 (30% EtOAc/petroleum ether); m.p. 142-144 °C (EtOAc/petroleum ether); $[\alpha]_D^{24} +94.5$ (c 0.55, CHCl₃); IR (film) 2974, 2930, 1711 (C=O), 1600, 1504, 1365, 1248, 1170, 1047, 830 cm⁻¹; ¹H NMR (500 MHz, (CD₃)₂CO) δ 8.15 (1H, d, J = 8.4 Hz, ArH), 8.03 (1H, d, J = 8.4 Hz, ArH), 7.88 (1H, d, J = 8.0 Hz, ArH), 7.78-7.73 (1H, m, ArH), 7.57-7.52 (1H, m, ArH), 7.26 (1H, d, ArH), 7.20 (2H, t, J = 8.0 Hz, ArH), 7.13-7.01 (3H, m, ArH and NH), 5.10-4.90 (1H, m, CHN), 3.61-3.46 (1H, m, CHCH₃), 2.24 (3H, s, ArCH₃), 1.33 (3H, d, J = 6.8 Hz, CHCH₃), 1.27 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, (CD₃)₂CO) δ 165.3 (C), 156.0 (C), 148.5 (C), 141.2 (C), 137.0 (CH), 136.8 (C), 130.2 (CH), 129.7 (CH),

129.5 (2 × CH), 128.6 (CH), 128.0 (C), 127.6 (2 × CH), 126.8 (CH), 122.8 (CH), 78.5 (C), 59.9 (CH), 48.2 (CH), 28.5 (3 × CH₃), 21.0 (CH₃), 19.6 (CH₃); HRMS (ESI) Exact mass calcd for C₂₄H₂₉N₂O₂ [M+H]⁺: 377.2229, found: 377.2228. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r (major) = 10.6, t_r (minor) = 15.9 min; 82% ee.



tert-Butyl N-[(1R,2S)-1-(2-chlorophenyl)-2-(quinolin-2-yl)propyl]carbamate (221c). The title compound was prepared according to General Procedure B from 2-

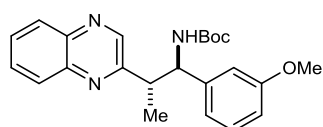
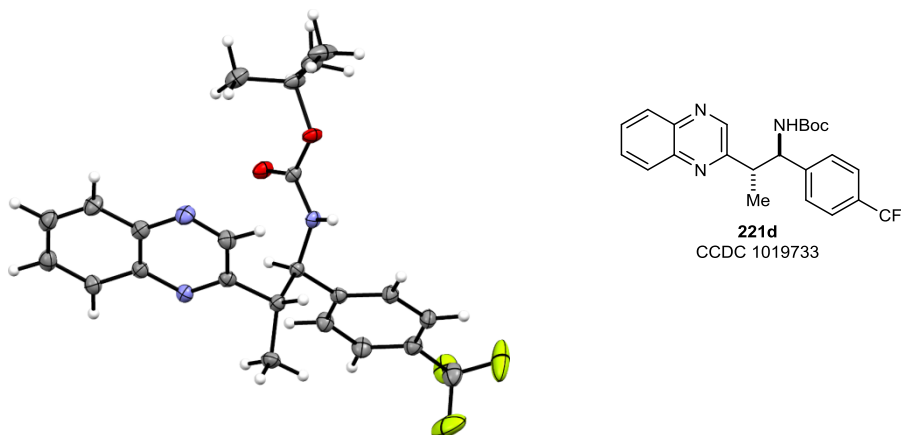
vinylquinoline (**175b**) (47 mg, 0.30 mmol) and *N*-Boc imine **206g** (79 mg, 0.33 mmol) and purified by column chromatography (0-10% EtOAc/petroleum ether) to give an orange oil (50 mg, 42%). R_f 0.65 (30% EtOAc/petroleum ether); [α]_D²² +189.1 (*c* 1.10, CHCl₃); IR (CHCl₃) 3062, 2930, 1709 (C=O), 1502, 1367, 1282, 1170, 1049, 881, 864 cm⁻¹; ¹H NMR (400 MHz, (CD₃)₂CO) δ 8.13 (1H, d, *J* = 8.4 Hz, ArH), 8.08 (1H, d, *J* = 8.5 Hz, ArH), 7.90 (1H, d, *J* = 8.1 Hz, ArH), 7.84-7.74 (1H, m, ArH), 7.58 (1H, t, *J* = 7.1 Hz, ArH), 7.50 (1H, d, *J* = 7.6 Hz, NH), 7.40 (1H, d, *J* = 7.9 Hz, ArH), 7.27-6.97 (4H, m, ArH), 5.56-5.44 (1H, m, CHN), 3.69-3.47 (1H, m, CHCH₃), 1.46 (3H, d, *J* = 6.9 Hz, CHCH₃), 1.32 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, (CD₃)₂CO) δ 164.4 (C), 156.0 (C), 148.3 (C), 141.6 (C), 137.3 (CH), 133.3 (C), 130.4 (CH), 130.1 (CH), 129.7 (CH), 129.1 (CH), 128.9 (CH), 128.7 (CH), 128.0 (C), 127.6 (CH), 127.0 (CH), 123.1 (CH), 78.9 (C), 57.0 (CH), 46.0 (CH), 28.5 (3 × CH₃), 19.4 (CH₃); HRMS (ESI) Exact mass calcd for C₂₃H₂₆ClN₂O₂ [M+H]⁺: 397.1677, found: 397.1645. Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (90:10 hexane:*i*-PrOH, 1.5 mL/min, 230 nm, 25 °C); t_r (minor) = 3.8, t_r (major) = 14.1 min; 85% ee.



tert-Butyl N-[(1R,2S)-2-(quinoxalin-2-yl)-1-[4-(trifluoromethyl)phenyl]propyl]carbamate (221d). The title compound was prepared according to General Procedure B from 2-vinylquinoxaline (**175d**) (47 mg, 0.30 mmol) and *N*-Boc imine

206h (90 mg, 0.33 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a white solid (59 mg, 46%). R_f 0.21 (20% EtOAc/petroleum ether); m.p. 167-169 °C (EtOAc/petroleum ether); $[\alpha]_D^{24} +103.7$ (c 1.06, CHCl_3); IR (film) 2979, 2938, 1701 (C=O), 1493, 1367, 1326, 1165, 1125, 1067, 848 cm^{-1} ; ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{CO}$) δ 8.78 (1H, s, ArH), 8.10 (1H, d, $J = 8.1$ Hz, ArH), 8.05 (1H, d, $J = 7.8$ Hz, ArH), 7.85 (1H, t, $J = 7.0$ Hz, ArH), 7.83-7.77 (1H, m, ArH), 7.69 (4H, s, ArH), 6.91 (1H, d, $J = 8.2$ Hz, NH), 5.23-5.14 (1H, m, CHN), 3.85-3.72 (1H, m, CHCH₃), 1.33 (3H, d, $J = 6.8$ Hz, CHCH₃), 1.17 (9H, s, C(CH₃)₃); ^{13}C NMR (125.8 MHz, $(\text{CD}_3)_2\text{CO}$) δ 159.6 (C), 155.8 (C), 148.2 (C), 147.2 (CH), 142.8 (C), 142.6 (C), 130.8 (CH), 130.2 (CH), 130.1 (CH), 129.9 (CH), 129.6 (C, q, $J = 32.5$ Hz), 128.8 (2 \times CH), 126.1 (2 \times CH, q, $J = 3.9$ Hz), 125.4 (C, q, $J = 270.6$ Hz), 79.0 (C), 60.0 (CH), 45.6 (CH), 28.3 (3 \times CH₃), 18.7 (CH₃); ^{19}F NMR (377 MHz, $(\text{CD}_3)_2\text{CO}$) δ -62.9; HRMS (ESI) Exact mass calcd for $\text{C}_{23}\text{H}_{25}\text{F}_3\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 432.1898, found: 432.1897. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r (minor) = 11.7, t_r (major) = 14.6 min; 93% ee.

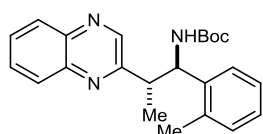
Slow diffusion of hexane into a solution of **221d** in EtOAc provided single crystals that were suitable for X-ray crystallography:



tert-Butyl *N*-[(1*R*,2*S*)-1-(3-methoxyphenyl)-2-(quinoxalin-2-yl)propyl]carbamate (**221e**). The title compound was prepared according to General Procedure

B from 2-vinylquinoxaline (**175d**) (47 mg, 0.30 mmol) and *N*-Boc imine **206l** (78

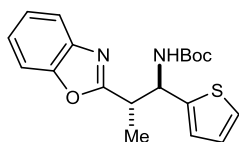
mg, 0.33 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a white solid (69 mg, 59%). R_f 0.52 (20% EtOAc/petroleum ether); m.p. 134-136 °C (EtOAc/petroleum ether); $[\alpha]_D^{24} +115.7$ (c 1.14, CHCl_3); IR (film) 2975, 2930, 1699 (C=O), 1601, 1492, 1366, 1253, 1045, 762, 699 cm^{-1} ; ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{CO}$) δ 8.77 (1H, s, ArH), 8.09 (1H, d, $J = 8.1$ Hz, ArH), 8.04 (1H, d, $J = 8.1$ Hz, ArH), 7.83 (1H, t, $J = 7.1$ Hz, ArH), 7.80-7.75 (1H, m, ArH), 7.24 (1H, t, $J = 7.9$ Hz, ArH), 7.06 (1H, s, ArH), 7.01 (1H, d, $J = 7.5$ Hz, ArH), 6.83-6.79 (1H, m, ArH), 6.73 (1H, d, $J = 8.4$ Hz, NH), 5.15-4.91 (1H, m, CHN), 3.76 (3H, s, OCH_3), 3.75-3.67 (1H, m, CHCH_3), 1.32 (3H, d, $J = 7.0$ Hz, CHCH_3), 1.16 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (125.8 MHz, $(\text{CD}_3)_2\text{CO}$) δ 160.8 (C), 160.0 (C), 155.7 (C), 147.3 (CH), 145.0 (C), 142.8 (C), 142.5 (C), 130.7 (CH), 130.2 (CH), 130.02 (CH), 129.96 (CH), 129.86 (CH), 120.3 (CH), 113.5 ($2 \times \text{CH}$), 78.7 (C), 60.3 (CH), 55.4 (CH_3), 46.1 (CH), 28.4 ($3 \times \text{CH}_3$), 18.5 (CH_3); HRMS (ESI) Exact mass calcd for $\text{C}_{23}\text{H}_{28}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$: 394.2125, found: 394.2146. Enantiomeric excess was determined by HPLC with a Chiralpak IC column (70:30 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r (minor) = 8.8, t_r (major) = 15.6 min; 79% ee.



***tert*-Butyl *N*-[(1*R*,2*S*)-1-(2-methylphenyl)-2-(quinoxalin-2-yl)propyl]carbamate (221f).** The title compound was prepared according to General Procedure B from 2-

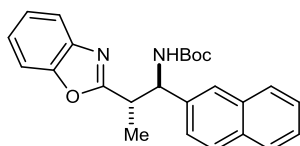
vinylquinoxaline (**175d**) (47 mg, 0.30 mmol) and *N*-Boc imine **206f** (72 mg, 0.33 mmol) and purified by column chromatography (10% EtOAc/*iso*-hexane) to give a pale yellow oil (63 mg, 56%). R_f 0.26 (20% EtOAc/petroleum ether); $[\alpha]_D^{24} +181.8$ (c 0.66, CHCl_3); IR (CHCl_3) 3010, 2981, 1708 (C=O), 1494, 1455, 1367, 1289, 1250, 1168, 924 cm^{-1} ; ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{CO}$) δ 8.78 (1H, s, ArH), 8.11 (1H, d, $J = 8.0$ Hz, ArH), 8.05 (1H, d, $J = 8.1$ Hz, ArH), 7.84 (1H, t, $J = 7.3$ Hz, ArH), 7.79 (1H, t, $J = 7.3$ Hz, ArH), 7.41-7.35 (1H, m, ArH), 7.24-7.18 (1H, m, ArH), 7.18-7.10 (2H, m, ArH), 6.67 (1H, d, $J = 8.2$ Hz, NH), 5.52-5.28 (1H, m, CHN), 3.80-3.65 (1H, m, CHCH_3), 2.57 (3H, s, Ar CH_3), 1.30 (3H, d, $J = 7.0$ Hz, CHCH_3), 1.12 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (125.8 MHz, $(\text{CD}_3)_2\text{CO}$) δ 160.1 (C), 155.7 (C), 147.4 (CH), 142.9 (C), 142.6 (C), 142.0 (C), 136.7 (C), 131.1 (CH), 130.7 (CH), 130.03 (CH), 129.97 (CH), 129.94 (CH), 127.7 (CH), 127.1 (CH), 126.9 (CH),

78.6 (C), 55.8 (CH), 45.8 (CH), 28.3 (3 × CH₃), 19.9 (CH₃), 17.9 (CH₃); HRMS (ESI) Exact mass calcd for C₂₃H₂₈N₃O₂ [M+H]⁺: 378.2176, found: 378.2168. Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (80:20 *iso*-hexane:*i*-PrOH, 1.5 mL/min, 230 nm, 25 °C); t_r (major) = 7.4, t_r (minor) = 18.4 min; 80% ee.



***tert*-Butyl *N*-[(1*R*,2*S*)-2-(1,3-benzothiazol-2-yl)-1-(thiophen-2-yl)propyl]carbamate (221g).** The title compound was prepared according to General Procedure B from 2-

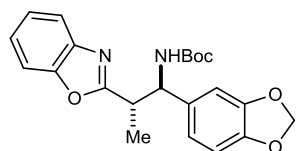
vinylbenzoxazole (**175l**) (44 mg, 0.30 mmol) and *N*-Boc imine **206i** (70 mg, 0.33 mmol) and purified by column chromatography (10% EtOAc/hexane) to give a yellow foam (77 mg, 71%). R_f 0.52 (20% EtOAc/petroleum ether); [α]_D²⁴ +11.6 (*c* 1.03, CHCl₃); IR (film) 2974, 2925, 1710 (C=O), 1616, 1567, 1533, 1456, 1241, 1183, 700, cm⁻¹; ¹H NMR (500 MHz, (CD₃)₂CO) δ 7.71-7.65 (1H, m, ArH), 7.60-7.55 (1H, m, ArH), 7.39-7.31 (2H, m, ArH), 7.28 (1H, d, *J* = 4.9 Hz, ArH), 7.07 (1H, d, *J* = 3.5 Hz, ArH), 6.98-6.89 (1H, m, ArH), 6.87-6.75 (1H, m, NH), 5.50-5.28 (1H, m, CHN), 3.86-3.66 (1H, m, CHCH₃), 1.44 (3H, d, *J* = 7.0 Hz, CHCH₃), 1.33 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, (CD₃)₂CO) δ 168.6 (C), 155.9 (C), 151.4 (C), 145.9 (C), 142.1 (C), 127.6 (CH), 125.7 (CH), 125.6 (CH), 125.2 (CH), 125.1 (CH), 120.4 (CH), 111.3 (CH), 79.4 (C), 54.6 (CH), 41.1 (CH), 28.5 (3 × CH₃), 16.7 (CH₃); HRMS (ESI) Exact mass calcd for C₁₉H₂₃N₂O₃S [M+H]⁺: 359.1424, found: 359.1426. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r (major) = 17.1, t_r (minor) = 27.1 min; 69% ee.



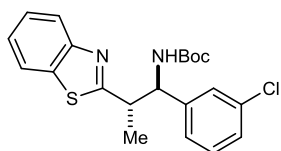
***tert*-Butyl *N*-[(1*R*,2*S*)-2-(1,3-benzoxazol-2-yl)-1-(naphthalen-2-yl)propyl]carbamate (221h).** The title compound was prepared according to General Procedure B

from 2-vinylbenzoxazole (**175l**) (44 mg, 0.30 mmol) and *N*-Boc imine **206d** (84 mg, 0.33 mmol) and purified by column chromatography (10% EtOAc/hexane) to give a white solid (76 mg, 63%). R_f 0.59 (20% EtOAc/petroleum ether); m.p. 142-144 °C (EtOAc/petroleum ether); [α]_D²² +64.1 (*c* 1.03, CHCl₃); IR (CHCl₃) 3009, 2983, 1710

(C=O), 1500, 1456, 1392, 1243, 1166, 927, 891 cm^{-1} ; ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{CO}$) δ 7.93 (1H, s, ArH), 7.91-7.82 (3H, m, ArH), 7.71-7.66 (1H, m, ArH), 7.64 (1H, dd, $J = 8.5, 1.7$ Hz, ArH), 7.59-7.52 (1H, m, ArH), 7.51-7.43 (2H, m, ArH), 7.38-7.29 (2H, m, ArH), 6.86 (1H, d, $J = 8.1$ Hz, NH), 5.28 (1H, t, $J = 8.3$ Hz, CHN), 3.85-3.68 (1H, m, CHCH₃), 1.37 (3H, s, CHCH₃), 1.25 (9H, s, C(CH₃)₃); ^{13}C NMR (128.5 MHz, $(\text{CD}_3)_2\text{CO}$) δ 168.9 (C), 155.8 (C), 151.5 (C), 142.3 (C), 139.8 (C), 134.3 (C), 133.8 (C), 129.1 (CH), 128.7 (CH), 128.5 (CH), 127.1 (CH), 127.0 (CH), 126.8 (CH), 125.8 (CH), 125.6 (CH), 125.0 (CH), 120.4 (CH), 111.3 (CH), 79.1 (C), 59.2 (CH), 40.9 (CH), 28.4 ($3 \times \text{CH}_3$), 17.2 (CH₃); HRMS (ESI) Exact mass calcd for $\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 425.1835, found: 425.1836. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r (major) = 13.5, t_r (minor) = 22.6 min; 81% ee.

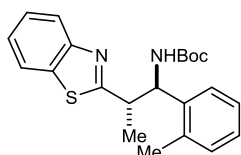


***tert*-Butyl *N*-[(1*R*,2*S*)-1-(2*H*-1,3-benzodioxol-5-yl)-2-(1,3-benzoxazol-2-yl)propyl]carbamate (221i).** The title compound was prepared according to General Procedure B from 2-vinylbenzoxazole (**175l**) (44 mg, 0.30 mmol) and *N*-Boc imine **206j** (82 mg, 0.33 mmol) and purified by column chromatography (0-25% EtOAc/petroleum ether) to give a colorless foam (93 mg, 78%). R_f 0.49 (30% EtOAc/petroleum ether); $[\alpha]_D^{22} +68.4$ (c 1.05, CHCl_3); IR (CHCl_3) 3008, 2982, 1710 (C=O), 1504, 1489, 1368, 1243, 1164, 1042, 933 cm^{-1} ; ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{CO}$) δ 7.71-7.64 (1H, m, ArH), 7.60-7.53 (1H, m, ArH), 7.38-7.29 (2H, m, ArH), 7.04 (1H, d, $J = 1.7$ Hz, ArH), 6.90 (1H, dd, $J = 8.0, 1.5$ Hz, ArH), 6.78 (1H, d, $J = 8.0$ Hz, ArH), 6.69 (1H, d, $J = 8.0$ Hz, NH), 5.97 (2H, s, CH₂), 5.01 (1H, t, $J = 8.7$ Hz, CHN), 3.59 (1H, app quin, $J = 7.1$ Hz, CHCH₃), 1.31 (3H, d, $J = 7.0$ Hz, CHCH₃), 1.23 (9H, s, C(CH₃)₃); ^{13}C NMR (100.6 MHz, $(\text{CD}_3)_2\text{CO}$) δ 169.0 (C), 155.7 (C), 151.5 (C), 148.8 (C), 147.8 (C), 142.3 (C), 136.4 (C), 125.5 (CH), 125.0 (CH), 121.5 (CH), 120.4 (CH), 111.3 (CH), 108.7 (CH), 108.0 (CH), 102.0 (CH₂), 79.0 (C), 58.8 (CH), 41.1 (CH), 28.4 ($3 \times \text{CH}_3$), 17.0 (CH₃); HRMS (ESI) Exact mass calcd for $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$: 397.1758, found: 397.1756. Enantiomeric excess was determined by HPLC with a Chiralpak IC column (95:5 hexane:*i*-PrOH, 1.5 mL/min, 230 nm, 25 °C); t_r (major) = 8.5, t_r (minor) = 9.3 min; 79% ee.



tert-Butyl N-[(1R,2S)-2-(1,3-benzothiazol-2-yl)-1-(3-chlorophenyl)propyl]carbamate (221j). The title compound was prepared according to General Procedure B

from 2-vinylbenzothiazole (**175k**) (47 mg, 0.30 mmol) and *N*-Boc imine **206b** (79 mg, 0.33 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a white solid (51 mg, 42%). R_f 0.45 (20% EtOAc/petroleum ether); m.p. 102-104 °C (EtOAc/petroleum ether); $[\alpha]_D^{24} +83.7$ (c 0.86, CHCl_3); IR (film) 2977, 1711 (C=O), 1498, 1453, 1369, 1284, 1253, 1167, 767 cm^{-1} ; ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{CO}$) δ 8.02-7.96 (2H, m, ArH), 7.54-7.48 (2H, m, ArH), 7.43-7.39 (1H, m, ArH), 7.38-7.36 (1H, m, ArH), 7.33 (1H, t, $J = 7.7$ Hz, ArH), 7.30-7.25 (1H, m, ArH), 6.87 (1H, d, $J = 7.1$ Hz, NH), 5.14-4.90 (1H, m, CHN), 3.95-3.67 (1H, m, CHCH₃), 1.39 (3H, d, $J = 6.8$ Hz, CHCH₃), 1.29 (9H, s, C(CH₃)₃); ^{13}C NMR (125.8 MHz, $(\text{CD}_3)_2\text{CO}$) δ 174.2 (C), 155.9 (C), 154.1 (C), 145.5 (CH), 135.6 (C), 134.6 (C), 130.8 (CH), 128.1 (CH), 127.9 (CH), 126.9 (CH), 126.5 (CH), 125.8 (CH), 123.5 (CH), 122.6 (CH), 79.2 (C), 59.9 (CH), 44.8 (CH), 28.5 (3 \times CH₃), 19.5 (CH₃); HRMS (ESI) Exact mass calcd for $\text{C}_{21}\text{H}_{24}\text{ClN}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 403.1242, found: 403.1242. Enantiomeric excess was determined by HPLC with a Chiralpak IC column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r (major) = 12.8, t_r (minor) = 16.9 min; 75% ee.

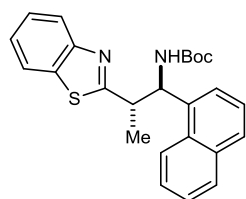
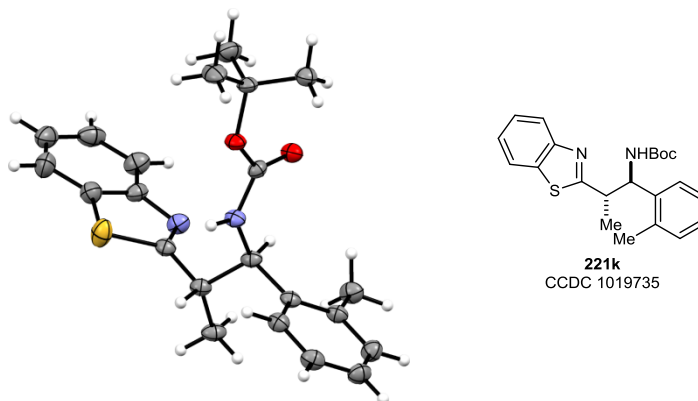


tert-Butyl N-[(1R,2S)-2-(1,3-benzothiazol-2-yl)-1-(2-methylphenyl)propyl]carbamate (221k). The title compound was prepared according to General Procedure B from 2-

vinylbenzothiazole (**175k**) (48 mg, 0.30 mmol) and *N*-Boc imine **206f** (72 mg, 0.33 mmol) and purified by column chromatography (5% EtOAc/hexane) to give a white solid (62 mg, 54%). R_f 0.59 (20% EtOAc/petroleum ether); m.p. 124-126 °C (EtOAc/petroleum ether); $[\alpha]_D^{24} +98.4$ (c 0.97, CHCl_3); IR (film) 2974, 1712 (C=O), 1500, 1456, 1365, 1245, 1170, 1013, 759, 729 cm^{-1} ; ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{CO}$) δ 8.00 (2H, t, $J = 8.8$ Hz, ArH), 7.55-7.48 (1H, m, ArH), 7.43-7.34 (2H, m, ArH), 7.23-7.15 (1H, m, ArH), 7.15-7.08 (2H, m, ArH), 6.79 (1H, d, $J = 7.1$ Hz, NH), 5.33 (1H, t, $J = 8.3$ Hz, CHN), 3.82-3.76 (1H, m, CHCH₃), 2.53 (3H, s, ArCH₃), 1.33 (3H, d, $J = 7.0$ Hz, CHCH₃), 1.23 (9H, s, C(CH₃)₃); ^{13}C NMR (125.8 MHz,

(CD₃)₂CO) δ 174.9 (C), 155.9 (C), 154.1 (CH), 141.6 (C), 136.4 (C), 135.7 (C), 131.0 (CH), 127.8 (C), 127.1 (CH), 126.84 (CH), 126.77 (CH), 125.7 (CH), 123.5 (CH), 122.6 (CH), 78.9 (C), 56.0 (CH), 44.9 (CH), 28.4 (3 \times CH₃), 19.8 (CH₃), 19.2 (CH₃); HRMS (ESI) Exact mass calcd for C₂₂H₂₇N₂O₂S [M+H]⁺: 383.1788, found: 383.1790. Enantiomeric excess was determined by HPLC with a Chiralpak IC column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); *t_r* (major) = 11.5, *t_r* (minor) = 16.2 min; 94% ee.

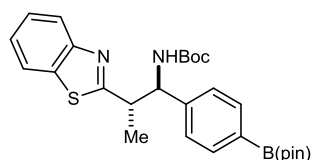
Slow diffusion of petroleum ether into a solution of **221k** in EtOAc provided single crystals that were suitable for X-ray crystallography:



tert-Butyl *N*-[(1*R*,2*S*)-2-(1,3-benzothiazol-2-yl)-1-(naphthalen-1-yl)propyl]carbamate (**221**). The title compound was prepared according to General Procedure B from 2-vinylbenzothiazole (**175k**) (55 mg, 0.30 mmol) and *N*-Boc imine **206e** (78 mg, 0.33 mmol) and purified by column chromatography (20-

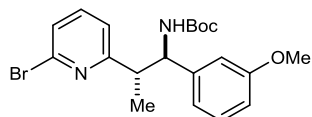
30% Et₂O/petroleum ether) to give a glassy foam (89 mg, 71%). *R_f* 0.71 (30% EtOAc/petroleum ether); [α]_D²² +143.4 (*c* 1.06, CHCl₃); IR (CHCl₃) 3066, 3011, 1709 (C=O), 1501, 1456, 1393, 1253, 1168, 1049, 952 cm⁻¹; ¹H NMR (400 MHz, (CD₃)₂CO) δ 8.41 (1H, d, *J* = 8.6 Hz, ArH), 8.04 (1H, d, *J* = 8.1 Hz, ArH), 7.94 (2H, t, *J* = 7.8 Hz, ArH), 7.81 (1H, d, *J* = 8.1 Hz, ArH), 7.68-7.61 (1H, m, ArH), 7.61-7.47 (3H, m, ArH), 7.46-7.32 (2H, m, ArH), 7.03 (1H, d, *J* = 8.0 Hz, NH), 6.05-5.85 (1H, m, CHN), 4.07-3.90 (1H, m, CHCH₃), 1.48 (3H, d, *J* = 6.5 Hz, CHCH₃), 1.29 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, (CD₃)₂CO) δ 174.4 (C), 156.0 (C), 154.2 (C), 139.1 (C), 135.5 (C), 134.8 (C), 132.1 (C), 129.8 (CH), 128.6 (CH), 127.2 (CH),

126.8 (CH), 126.5 (CH), 126.2 (CH), 125.8 (CH), 124.6 (CH), 124.0 (CH), 123.5 (CH), 122.5 (CH), 79.1 (C), 55.6 (CH), 44.8 (CH), 28.5 (3 × CH₃), 19.6 (CH₃); HRMS (ESI) Exact mass calcd for C₂₅H₂₇N₂O₂S [M+H]⁺: 419.1788, found: 419.1791. Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (90:10 hexane:*i*-PrOH, 1.5 mL/min, 230 nm, 25 °C); *t*_r (minor) = 7.2, *t*_r (major) = 15.1 min, 94% ee.



***tert*-Butyl *N*-[(1*R*,2*S*)-2-(1,3-benzothiazol-2-yl)-1-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]propyl]carbamate (221m).** The title compound

was prepared according to General Procedure B from 2-vinylbenzothiazole (**175k**) (48 mg, 0.30 mmol) and *N*-Boc imine **206k** (109 mg, 0.33 mmol) and purified by column chromatography (0-15% EtOAc/petroleum ether) to give a colorless foam (59 mg, 40%). *R*_f 0.50 (30% EtOAc/petroleum ether); [α]_D²² +97.4 (*c* 1.15, CHCl₃); IR (CHCl₃) 2982, 2932, 1710 (C=O), 1612, 1500, 1362, 1258, 1167, 980, 858 cm⁻¹; ¹H NMR (400 MHz, (CD₃)₂CO) δ 7.99 (1H, d, *J* = 8.2 Hz, ArH), 7.96 (1H, d, *J* = 8.0 Hz, ArH), 7.68 (2H, d, *J* = 7.8 Hz, ArH), 7.53-7.46 (1H, m, ArH), 7.44-7.36 (3H, m, ArH), 6.84 (1H, d, *J* = 8.5 Hz, NH), 5.16-4.97 (1H, m, CHN), 3.88-3.70 (1H, m, CHCH₃), 1.39 (3H, d, *J* = 6.9 Hz, CHCH₃), 1.32 (12H, s, 2 × C(CH₃)₂), 1.29 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, (CD₃)₂CO) δ 174.5 (C), 155.9 (C), 154.1 (C), 146.1 (C), 135.5 (2 × CH), 127.2 (2 × CH), 126.8 (CH), 125.8 (CH), 123.4 (CH), 122.6 (CH), 115.9 (C), 84.5 (2 × C), 79.0 (C), 60.3 (CH), 45.0 (CH), 28.5 (3 × CH₃), 25.2 (4 × CH₃), 19.6 (CH₃), the carbon next to boron was not observed due to quadrupolar relaxation effects of ¹¹B; HRMS (ESI) Exact mass calcd for C₂₇H₃₆BN₂O₄S [M+H]⁺: 495.2483, found: 495.2499. Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (95:5 hexane:*i*-PrOH, 1.5 mL/min, 254 nm, 25 °C); *t*_r (minor) = 18.3, *t*_r (major) = 40.1 min, 86% ee.



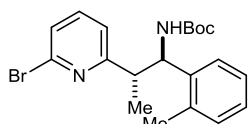
***tert*-Butyl *N*-[(1*R*,2*S*)-2-(6-bromopyridin-2-yl)-1-(4-methoxyphenyl)propyl]carbamate (221n).** The title compound was prepared according to General Procedure B from 6-bromo-

2-vinylpyridine (**175p**) (55 mg, 0.30 mmol) and *N*-Boc imine **206l** (78 mg, 0.33

mmol) and purified by column chromatography (20-30% Et₂O/petroleum ether) to give a 4.7:1 mixture of diastereomers as a white solid (89 mg, 71%). R_f 0.39 (30% EtOAc/petroleum ether); m.p. 138-142 °C (EtOAc/petroleum ether); [α]_D²⁴ +88.5 (c 1.04, CHCl₃); IR (CHCl₃) 3008, 2981, 1709 (C=O), 1602, 1498, 1367, 1259, 1164, 1045, 858 cm⁻¹; HRMS (ESI) Exact mass calcd for C₂₀H₂₆BrN₂O₅ [M+COOH]⁺: 465.1032, found: 465.1031. Enantiomeric excess was determined by HPLC with a Chiralpak IA-3 column (90:10 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); major diastereomer: t_r (major) = 5.9, t_r (minor) = 19.6 min, 80% ee; minor diastereomer: t_r (minor) = 8.8, t_r (major) = 13.3 min, 5% ee.

Major diastereomer: ¹H NMR (400 MHz, (CD₃)₂CO) δ 7.60 (1H, t, *J* = 7.7 Hz, ArH), 7.42 (1H, d, *J* = 8.0 Hz, ArH), 7.27-7.20 (2H, m, ArH), 7.01-6.97 (1H, m, ArH), 6.96-6.91 (1H, m, ArH), 6.83-6.76 (1H, m, ArH), 6.60 (1H, d, *J* = 8.2 Hz, NH), 4.89 (1H, t, *J* = 8.9 Hz, CHN), 3.78 (3H, s, OCH₃), 3.41-3.27 (1H, m, CHCH₃), 1.27 (9H, s, C(CH₃)₃), 1.14 (3H, d, *J* = 6.8 Hz, CHCH₃); ¹³C NMR (125.6 MHz, (CD₃)₂CO) δ 166.3 (C), 160.7 (C), 155.7 (C), 145.1 (C), 141.8 (C), 140.1 (CH), 130.0 (CH), 126.7 (CH), 123.2 (CH), 120.2 (CH), 113.4 (CH), 113.3 (CH), 78.6 (C), 60.1 (CH), 55.4 (CH₃), 47.6 (CH), 28.5 (3 × CH₃), 19.0 (CH₃).

Diagnostic peaks for minor diastereomer: ¹H NMR (400 MHz, (CD₃)₂CO) δ 7.46 (1H, d, *J* = 7.7, ArH), 7.31 (1H, d, *J* = 7.3 Hz, ArH), 7.08 (1H, t, *J* = 7.8 Hz, ArH), 7.02 (1H, d, *J* = 7.4 Hz, ArH), 6.66 (1H, dd, *J* = 8.2, 1.7 Hz, ArH), 5.03 (1H, t, *J* = 9.3 Hz, CHN), 3.70 (3H, s, OCH₃), 1.39-1.32 (12H, m, CH₃ and C(CH₃)₃); ¹³C NMR (125.6 MHz, (CD₃)₂CO) δ 165.9 (C), 160.4 (C), 156.1 (C), 145.0 (C), 141.7 (C), 139.9 (CH), 130.2 (CH), 129.7 (CH), 126.5 (CH), 123.1 (CH), 113.6 (CH), 113.2 (CH), 78.7 (C), 60.0 (CH), 55.3 (CH₃), 48.2 (CH), 28.6 (3 × CH₃), 17.6 (CH₃).



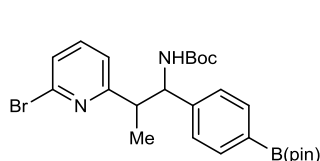
tert-Butyl N-[(1*R*,2*S*)-2-(6-bromopyridin-2-yl)-1-(2-methylphenyl)propyl]carbamate (221o). The title compound was prepared according to General Procedure C from 6-bromo-

2-vinylpyridine (**175p**) (55 mg, 0.30 mmol) and *N*-Boc imine **206f** (72 mg, 0.33 mmol) and purified by column chromatography (0-10% EtOAc/ petroleum ether) to give a 3.1 mixture of diastereomers as a pale yellow foam (67 mg, 55%). R_f 0.60

(30% EtOAc/petroleum ether); $[\alpha]_{\text{D}}^{22} +59.1$ (c 1.32, CHCl_3); IR (CHCl_3) 3009, 2979, 2931, 1709 ($\text{C}=\text{O}$), 1500, 1367, 1253, 1164, 1044, 919 cm^{-1} ; HRMS (ESI) Exact mass calcd for $\text{C}_{20}\text{H}_{25}\text{BrN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 405.1172, found: 405.1155. Enantiomeric excess was determined by HPLC with a Chiralpak IC column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 210 nm, 25 °C); major diastereomer: t_{r} (major) = 11.6, t_{r} (minor) = 19.5 min, 79% ee; minor diastereomer: t_{r} (minor) = 14.7, t_{r} (major) = 21.1 min, 57% ee.

Major diastereomer: ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{CO}$) δ 7.61 (1H, t, J = 7.7 Hz, ArH), 7.45 (1H, t, J = 8.4 Hz, ArH), 7.35-7.31 (1H, m, ArH), 7.26 (1H, d, J = 7.6 Hz, ArH), 7.21-7.12 (2H, m, ArH), 7.00-6.90 (1H, m, ArH), 6.55 (1H, d, J = 7.3 Hz, NH), 5.24 (1H, t, J = 9.1 Hz, CHN), 3.41-3.23 (1H, m, CHCH_3), 2.51 (3H, s, ArCH₃), 1.24 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.12 (3H, d, J = 6.9 Hz, CHCH_3); ^{13}C NMR (125.8 MHz, $(\text{CD}_3)_2\text{CO}$) δ 166.3 (C), 155.7 (C), 142.2 (C), 141.9 (C), 140.0 (CH), 139.8 (CH), 136.5 (C), 130.9 (CH), 127.5 (CH), 127.0 (CH), 126.7 (CH), 123.2 (CH), 78.6 (C), 55.5 (CH), 47.8 (CH), 28.5 ($3 \times \text{CH}_3$), 19.9 (CH_3), 18.4 (CH_3).

Minor diastereomer: ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{CO}$) δ 7.31 (1H, t, J = 7.7 Hz, ArH), 7.10-7.04 (1H, m, ArH), 6.49-6.42 (1H, m, NH), 5.36 (1H, t, J = 9.5 Hz, HN), 3.49-3.40 (1H, m, CHCH_3), 2.34 (3H, s, ArCH₃), 1.39-1.34 (12H, m, CHCH_3 and $\text{C}(\text{CH}_3)_3$ (assignments made where possible); ^{13}C NMR (125.8 MHz, $(\text{CD}_3)_2\text{CO}$) δ 165.9 (C), 156.3 (C), 141.8 (C), 130.7 (CH), 127.4 (CH), 127.3 (CH), 126.9 (CH), 126.8 (CH), 126.5 (CH), 123.3 (CH), 78.7 (C), 55.2 (CH), 47.5 (CH), 28.6 ($3 \times \text{CH}_3$), 19.7 (CH_3), 18.2 (CH_3).



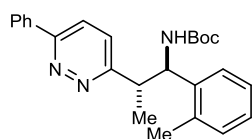
***tert*-Butyl *N*-[2-(6-bromopyridin-2-yl)-1-[4-(tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]propyl]carbamate (221p).** The title compound

was prepared according to General Procedure C from 6-bromo-2-vinylpyridine (**175p**) (55 mg, 0.30 mmol) and *N*-Boc imine **206k** (109 mg, 0.33 mmol) and purified by column chromatography (0-22% EtOAc/petroleum ether) to give a 1.6:1 mixture of diastereomers as a colorless foam (86 mg, 56%). R_{f} 0.29 (20% EtOAc/petroleum ether); $[\alpha]_{\text{D}}^{22} +55.2$ (c 1.015, CHCl_3); IR (CHCl_3) 3049, 3008, 1701 ($\text{C}=\text{O}$), 1612, 1583, 1499, 1362, 1163, 1143, 858 cm^{-1} ; HRMS (ESI) Exact mass calcd for $\text{C}_{25}\text{H}_{35}\text{BBrN}_2\text{O}_4$ $[\text{M}+\text{H}]^+$: 517.1868, found: 517.1857. Enantiomeric

excess was determined by HPLC with a Chiralpak AD-H column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); major diastereomer: t_r (major) = 25.9, t_r (major) = 48.7 min, 85% ee; minor diastereomer: t_r (major) = 29.8 min, t_r (minor) = 38.6 min, 0% ee.

Major diastereomer: ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{CO}$) δ 7.69 (2H, d, J = 7.6 Hz, ArH), 7.57 (2H, d, J = 7.9 Hz, ArH), 7.43 (1H, dd, J = 12.6, 7.8 Hz, ArH), 7.38 (1H, d, J = 7.9 Hz, ArH), 7.23 (1H, d, J = 8.0 Hz, ArH), 6.65 (1H, d, J = 4.7 Hz, NH), 4.94 (1H, t, J = 8.7 Hz, CHN), 3.45-3.30 (1H, m, CHCH₃), 1.39-1.38 (3H, m, CHCH₃), 1.33 (12H, s, $2 \times \text{C}(\text{CH}_3)_2$), 1.30 (9H, s, $\text{C}(\text{CH}_3)_3$); ^{13}C NMR (125.8 MHz, $(\text{CD}_3)_2\text{CO}$) δ 166.1 (C), 155.7 (C), 146.8 (C), 141.8 (C), 140.1 (CH), 135.5 ($2 \times \text{CH}$), 127.4 ($2 \times \text{CH}$), 126.7 (CH), 123.2 (CH), 84.4 ($2 \times \text{C}$), 78.7 (C), 60.2 (CH), 47.3 (CH), 28.5 ($3 \times \text{CH}_3$), 25.2 ($4 \times \text{CH}_3$), 19.1 (CH₃), the carbon next to boron was not observed due to quadrupolar relaxation effects of ^{11}B .

Minor diastereomer: ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{CO}$) δ 7.69 (1H, d, J = 7.6 Hz, ArH), 7.57 (1H, d, J = 7.9 Hz, ArH), 7.43 (1H, dd, J = 12.6, 7.8 Hz, ArH), 7.38 (1H, d, J = 7.9 Hz, ArH), 7.31 (1H, J = 7.6 Hz, ArH), 7.24 (1H, d, J = 8.0 Hz, ArH), 7.03 (1H, 7.5 Hz, ArH), 6.65 (1H, d, J = 4.7 Hz, CNH), 5.08 (1H, t, J = 9.3 Hz, CHN), 3.45-3.30 (1H, m, CHCH₃), 1.38-1.33 (12H, m, CHCH₃ and $\text{C}(\text{CH}_3)_3$), 1.28 (12H, s, $2 \times \text{C}(\text{CH}_3)_2$); $(\text{CD}_3)_2\text{CO}$) δ 165.7 (C), 156.1 (C), 146.7 (C), 141.7 (C), 139.9 (CH), 135.2 ($2 \times \text{CH}$), 127.5 ($2 \times \text{CH}$), 126.5 (CH), 123.1 (CH), 84.4 ($2 \times \text{C}$), 78.8 (C), 60.0 (CH), 47.8 (CH), 28.6 ($3 \times \text{CH}_3$), 25.2 ($4 \times \text{CH}_3$), 17.5 (CH₃), the carbon next to boron was not observed due to quadrupolar relaxation effects of ^{11}B .



tert-Butyl

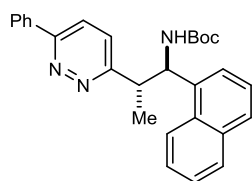
***N*-[(1*R*,2*S*)-1-(2-methylphenyl)-2-(6-**

phenylpyridazin-3-yl)propyl]carbamate (221q). The title

compound was prepared according to General Procedure B

from 3-phenyl-6-vinylpyridazine (**175o**) (55 mg, 0.30 mmol) and *N*-Boc imine **206f** (72 mg, 0.33 mmol) and purified by column chromatography (0-20% EtOAc/petroleum ether) to give a white solid (62 mg, 51%). R_f 0.23 (20% EtOAc/petroleum ether); m.p. 168-170 °C (EtOAc/petroleum ether); $[\alpha]_D^{22}$ +85.2 (c 0.92, CHCl_3); IR (film) 2972, 1700 (C=O), 1495, 1424, 1291, 1249, 1171, 753, 694 cm^{-1} ; ^1H NMR (400 MHz, $(\text{CD}_3)_2\text{CO}$) δ 8.27-8.16 (2H, m, ArH), 8.05 (1H, d, J = 8.8

Hz, ArH), 7.66-7.49 (4H, m, ArH), 7.42-7.32 (1H, m, ArH), 7.25-7.10 (3H, m, ArH), 6.77 (1H, d, $J = 8.4$ Hz, NH), 5.40 (1H, t, $J = 8.7$ Hz, CHN), 3.74-3.53 (1H, m, CHCH₃), 2.57 (3H, s, ArCH₃), 1.32 (3H, d, $J = 7.0$ Hz, CHCH₃), 1.24 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, (CD₃)₂CO) δ 165.0 (C), 158.3 (C), 155.8 (C), 142.0 (C), 137.7 (C), 136.5 (C), 131.0 (CH), 130.6 (CH), 129.8 (2 \times CH), 128.0 (CH), 127.6 (2 \times CH), 127.1 (CH), 126.9 (CH), 124.5 (CH), 78.7 (C), 55.6 (CH), 55.5 (CH), 46.2 (CH), 28.5 (3 \times CH₃), 19.9 (CH₃), 18.6 (CH₃); HRMS (ESI) Exact mass calcd for C₂₅H₃₀N₃O₂ [M+H]⁺: 377.2229, found: 377.2228. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 230 nm, 25 °C); t_r (major) = 12.4, t_r (minor) = 14.3 min; 74% ee.



tert-Butyl

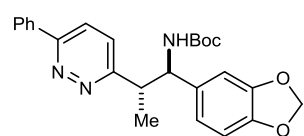
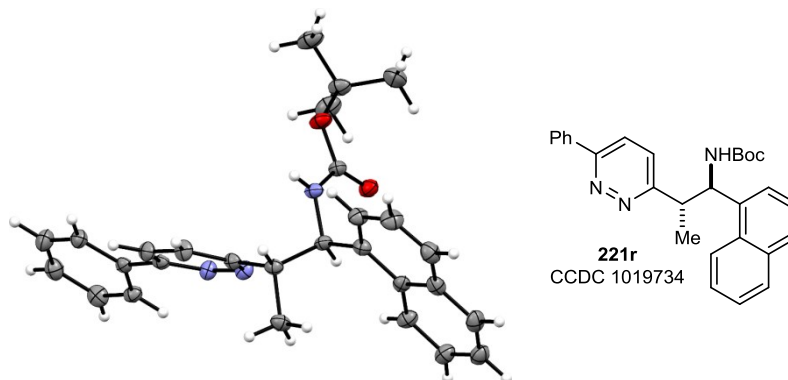
***N*-[(1*R*,2*S*)-1-(naphthalen-1-yl)-2-(6-**

phenylpyridazin-3-yl)propyl]carbamate (221r). The title

compound was prepared according to General Procedure B from 3-phenyl-6-vinylpyridazine (**175o**) (55 mg, 0.30 mmol)

and *N*-Boc imine **206e** (84 mg, 0.33 mmol) and purified by column chromatography (0-18% EtOAc/petroleum ether) to give a white solid (46 mg, 35%). R_f 0.37 (30% EtOAc/petroleum ether); m.p. 182-184 °C (EtOAc/petroleum ether); $[\alpha]_D^{22} +213.9$ (c 1.01, CHCl₃); IR (CHCl₃) 3008, 2982, 1709 (C=O), 1499, 1428, 1168, 861, 851 cm⁻¹; ¹H NMR (400 MHz, (CD₃)₂CO) δ 8.49 (1H, d, $J = 8.5$ Hz, ArH), 8.18 (2H, d, $J = 6.9$ Hz, ArH), 7.95 (2H, d, $J = 7.7$ Hz, ArH), 7.80 (1H, d, $J = 8.0$ Hz, ArH), 7.64 (1H, ddd, $J = 8.4, 6.8, 1.3$ Hz, ArH), 7.59-7.46 (5H, m, ArH), 7.45-7.33 (2H, m, ArH), 7.04 (1H, d, $J = 8.4$ Hz, NH), 6.00 (1H, t, $J = 8.2$ Hz, CHN), 3.95-3.69 (1H, m, CHCH₃), 1.43 (3H, d, $J = 6.7$ Hz, CHCH₃), 1.26 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, (CD₃)₂CO) δ 164.9 (C), 158.3 (C), 155.9 (C), 139.6 (C), 137.6 (C), 134.8 (C), 132.3 (C), 130.6 (CH), 129.8 (2 \times CH), 129.7 (CH), 128.4 (CH), 128.3 (CH), 127.7 (2 \times CH), 127.1 (CH), 126.5 (CH), 126.2 (CH), 124.7 (CH), 124.5 (CH), 124.2 (CH), 78.9 (C), 55.3 (CH), 46.2 (CH), 28.5 (3 \times CH₃), 19.1 (CH₃); HRMS (ESI) Exact mass calcd for C₂₈H₃₀N₃O₂ [M+H]⁺: 440.2333, found: 440.2319. Enantiomeric excess was determined by HPLC with a Chiralpak IC column (95:5 hexane:*i*-PrOH, 1.5 mL/min, 280 nm, 25 °C); t_r (minor) = 22.6, t_r (major) = 30.2 min; 88% ee.

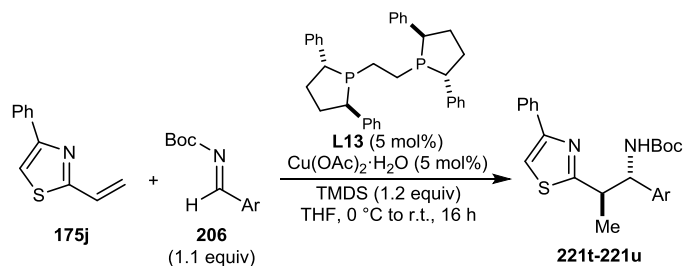
Slow diffusion of petroleum ether into a solution of **221r** in EtOAc provided single crystals that were suitable for X-ray crystallography:



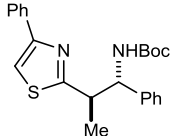
***tert*-Butyl *N*-[(1*R*,2*S*)-1-(2*H*-1,3-benzodioxol-5-yl)-2-(6-phenylpyridazin-3-yl)propyl]carbamate (**221s**).** The title compound was prepared according to General Procedure B

from 3-phenyl-6-vinylpyridazine (**175o**) (55 mg, 0.30 mmol) and *N*-Boc imine **206j** (82 mg, 0.33 mmol) and purified by column chromatography (0-25% EtOAc/petroleum ether) to give a white solid (65 mg, 50%). R_f 0.29 (30% EtOAc/petroleum ether); m.p. 216-218 °C (EtOAc/petroleum ether); $[\alpha]_D^{22} +116.8$ (c 1.01, CHCl₃); IR (CHCl₃) 3008, 2982, 1708 (C=O), 1504, 1490, 1368, 1249, 1169, 1042, 937 cm⁻¹; ¹H NMR (400 MHz, (CD₃)₂CO) δ 8.21-8.14 (2H, m, ArH), 8.04 (1H, d, J = 8.8 Hz, ArH), 7.66-7.44 (4H, m, ArH), 7.01 (1H, d, J = 1.5 Hz, ArH), 6.88 (1H, dd, J = 8.0, 1.4 Hz, ArH), 6.78 (1H, d, J = 8.0 Hz, ArH), 6.75 (1H, d, J = 9.3 Hz, NH), 5.97 (2H, s, CH₂), 4.97 (1H, t, J = 9.0 Hz, CHN), 3.70-3.48 (1H, m, CHCH₃), 1.30 (3H, d, J = 7.0 Hz, CHCH₃), 1.24 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, (CD₃)₂CO) δ 165.1 (C), 158.2 (C), 155.8 (C), 148.7 (C), 147.5 (C), 137.6 (C), 137.5 (C), 130.6 (CH), 129.8 (2 \times CH), 127.8 (CH), 127.6 (2 \times CH), 124.6 (CH), 121.4 (CH), 108.6 (CH), 108.1 (CH), 101.9 (CH₂), 78.7 (C), 59.9 (CH), 46.7 (CH), 28.5 (3 \times CH₃), 19.2 (CH₃); HRMS (ESI) Exact mass calcd for C₂₅H₂₈N₃O₄ [M+H]⁺: 434.2074, found: 434.2068. Enantiomeric excess was determined by HPLC with a Chiralpak IB-3 column (98:2 hexane:*i*-PrOH, 1.5 mL/min, 230 nm, 25 °C); t_r (minor) = 19.9, t_r (major) = 25.6 min; 59% ee.

General Procedure C: Reductive Coupling of Vinylazaarene **184j** with *N*-Boc Imines Using Ligand **L13**

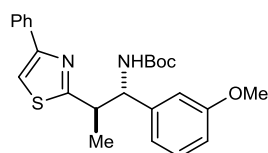
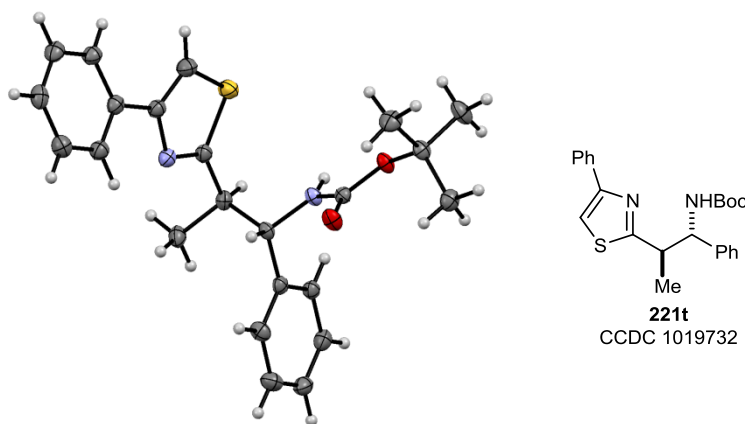


A solution of the appropriate vinylazaarene (0.30 mmol), Cu(OAc)₂·H₂O (3.0 mg, 0.015 mmol), (*R,R*)-Ph-BPE (**L13**) (7.5 mg, 0.015 mmol), and the appropriate imine (0.33 mmol) in THF (1.5 mL) was stirred at 0 °C for 15 min. TMDS (64 µL, 0.36 mmol) was then added dropwise over 1 min. The mixture was stirred at 0 °C for 1 h, then at room temperature for 15 h. The reaction was quenched carefully with SiO₂, and the resulting suspension was stirred for 15 min before being filtered through a short plug of SiO₂ using EtOAc as eluent and concentrated *in vacuo*. Purification of the residue by flash column chromatography gave the reductive coupling product.

 **tert-Butyl** *N*-[(1*S*,2*R*)-1-phenyl-2-(4-phenyl-1,3-thiazol-2-yl)propyl]carbamate (**221t**). The title compound was prepared according to General Procedure C from 4-phenyl-2-vinylthiazole (**175j**) (56 mg, 0.30 mmol) and *N*-Boc imine **206a** (68 mg, 0.33 mmol) and purified by column chromatography (1% Et₃N, 9.9% EtOAc, 89.1% hexane) to give a white solid (104 mg, 88%). R_f 0.40 (20% EtOAc/petroleum ether); m.p. 119-121 °C (EtOAc/petroleum ether); [α]_D²⁴ -66.6 (*c* 0.47, CHCl₃); IR (film) 2973, 1712 (C=O), 1494, 1454, 1366, 1220, 1169, 1030, 772, 699 cm⁻¹; ¹H NMR (500 MHz, (CD₃)₂CO) δ 8.06-8.02 (2H, m, ArH), 7.74 (1H, s, SCH), 7.50-7.44 (2H, m, ArH), 7.40-7.35 (3H, m, ArH), 7.32 (2H, t, *J* = 7.2 Hz, ArH), 7.25-7.22 (1H, m, ArH), 7.00-6.85 (1H, m, NH), 5.10-5.00 (1H, m, CHN), 3.82-3.70 (1H, m, CHCH₃), 1.40 (3H, d, *J* = 7.0 Hz, CHCH₃), 1.35 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, (CD₃)₂CO) δ 173.3 (C), 156.0 (C), 155.5 (C), 143.2 (C), 135.7 (C), 129.6 (2 × CH), 129.1 (2 × CH), 128.8 (CH), 127.9 (CH), 127.8 (2 × CH), 127.1 (2 × CH), 113.3 (CH), 78.9 (C), 60.4 (CH), 44.5 (CH), 28.6 (3 × CH₃), 19.8 (CH₃); HRMS (ESI) Exact mass calcd for C₂₃H₂₇N₂O₂S [M+H]⁺: 395.1788, found: 395.1787. Enantiomeric excess was

determined by HPLC with a Chiralpak IC column (98:2 hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 °C); t_r (minor) = 14.7 min, t_r (major) = 21.7 min; 87% ee.

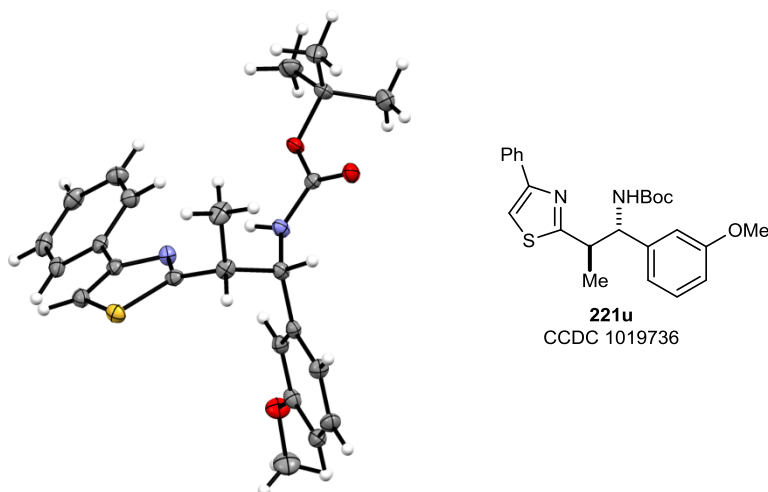
Slow diffusion of petroleum ether into a solution of **221t** in EtOAc provided single crystals that were suitable for X-ray crystallography:



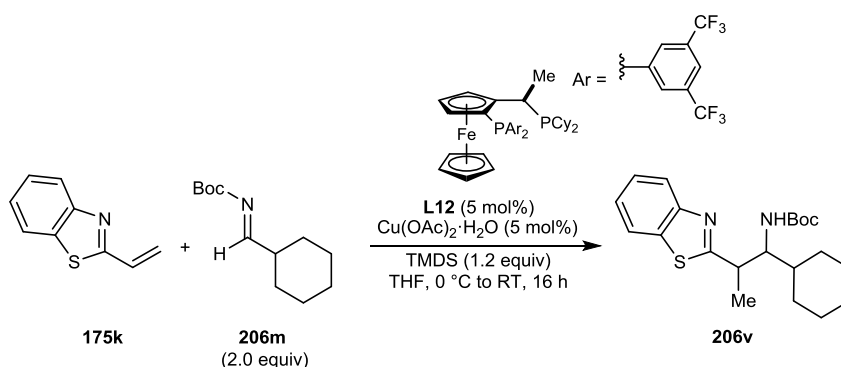
***tert*-Butyl *N*-[(1*S*,2*R*)-1-(3-methoxyphenyl)-2-(4-phenyl-1,3-thiazol-2-yl)propyl]carbamate (**221u**).** The title compound was prepared according to General Procedure C

from 4-phenyl-2-vinylthiazole (**175j**) (56 mg, 0.30 mmol) and *N*-Boc imine **206l** (78 mg, 0.33 mmol) and purified by column chromatography (1% Et₃N in 10% EtOAc/hexane) to give a white solid (106 mg, 83%). R_f 0.62 (30% EtOAc/petroleum ether); m.p. 132-136 °C (EtOAc/petroleum ether); $[\alpha]_D^{24}$ -59.4 (c 1.01, CHCl₃); IR (film) 2975, 2931, 1710 (C=O), 1601, 1490, 1365, 1263, 1167, 1041, 693 cm⁻¹; ¹H NMR (400 MHz, (CD₃)₂CO) δ 8.04-8.00 (2H, m, ArH), 7.73 (1H, s, ArH), 7.49-7.41 (2H, m, ArH), 7.38-7.32 (1H, m, ArH), 7.21 (1H, t, J = 7.9 Hz, ArH), 7.00-6.83 (3H, m, ArH), 6.79 (1H, dd, J = 8.2, 2.0 Hz, NH), 5.05-4.80 (1H, m, CHN), 3.78-3.70 (1H, m, CHCH₃), 3.76 (3H, s, OCH₃), 1.38 (3H, d, J = 7.0 Hz, CHCH₃), 1.33 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz, (CD₃)₂CO) δ 173.4 (C), 160.8 (C), 156.0 (C), 155.5 (C), 144.7 (C), 135.7 (C), 130.1 (CH), 129.6 (2 \times CH), 128.8 (CH), 127.1 (2 \times CH), 120.0 (CH), 113.5 (CH), 113.34 (CH), 113.29 (CH), 78.9 (C), 60.3 (CH), 55.4 (CH₃), 44.4 (CH), 28.6 (3 \times CH₃), 19.7 (CH₃); HRMS (ESI) Exact mass calcd for C₂₄H₂₉N₂O₃S [M+H]⁺: 425.1892, found: 425.1890. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (95:5 hexane:*i*-PrOH, 0.8 mL/min, 254 nm, 25 °C); t_r (minor) = 16.0, t_r (major) = 18.8 min; 78% ee.

Slow diffusion of hexane into a solution of **221u** in EtOAc provided single crystals that were suitable for X-ray crystallography:



***tert*-Butyl *N*-[2-(1,3-benzothiazol-2-yl)-1-cyclohexylpropyl]carbamate (**221v**)**



A solution of 2-vinylbenzothiazole (**184k**) (48 mg, 0.30 mmol), $\text{Cu}(\text{OAc})_2\cdot\text{H}_2\text{O}$ (3.0 mg, 0.015 mmol), SL-J006-1 (**L3**) (13 mg, 0.015 mmol), and *N*-Boc imine **215m** (127 mg, 0.60 mmol) in THF (1.5 mL) was stirred at 0 °C for 15 min. TMSD (64 μL , 0.36 mmol) was then added dropwise over 1 min. The mixture was stirred at 0 °C for 1 h, then at room temperature for 15 h. The reaction was quenched carefully with SiO_2 , and the resulting suspension was stirred for 15 min before being filtered through a short plug of SiO_2 , using EtOAc as eluent and concentrated *in vacuo* and purified by column chromatography (0-10% EtOAc/petroleum ether) to give the major diastereomer of **5u** as a yellow oil (81 mg, 73%) followed by the minor diastereomer of **5u** as a pale yellow oil (18 mg, 16%).

Major diastereomer: R_f 0.40 (20% EtOAc/petroleum ether); $[\alpha]_D^{22} +22.9$ (c 0.87, CHCl_3); IR (CHCl_3) 2931, 2855, 1708 ($\text{C}=\text{O}$), 1504, 1451, 1438, 1367, 1242, 1170, 978 cm^{-1} ; ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{CO}$) δ 8.01 (1H, d, $J = 8.0$ Hz, ArH), 7.96 (1H, d, $J = 7.8$ Hz, ArH), 7.50 (1H, ddd, $J = 8.3, 7.3, 1.2$ Hz, ArH), 7.41 (1H, td, $J = 7.8, 1.1$ Hz, ArH), 5.99 (1H, d, $J = 9.6$ Hz, NH), 3.75-3.66 (2H, m, CHN and CHCH₃), 1.90 (1H, d, $J = 11.7$ Hz, CH₂), 1.81 (1H, d, $J = 12.2$ Hz, CH₂), 1.74-1.66 (3H, m, CH₂), 1.62-1.56 (1H, m, CH₂), 1.43 (3H, d, $J = 6.8$ Hz, CHCH₃), 1.40-1.37 (10H, m, CHCH₂ and C(CH₃)₃), 1.21-1.06 (4H, m, CH₂); ^{13}C NMR (125.8 MHz, $(\text{CD}_3)_2\text{CO}$) δ 174.9 (C), 157.0 (C), 154.1 (C), 135.4 (C), 126.8 (CH), 125.7 (CH), 123.4 (CH), 122.6 (CH), 78.5 (C), 60.3 (CH), 41.4 (CH), 40.3 (CH), 31.3 (CH₂), 29.8 (CH₂), 28.6 ($3 \times \text{CH}_3$), 27.10 (CH₂), 26.71 (CH₂), 26.69 (CH₂), 19.9 (CH₃). HRMS (ESI) Exact mass calcd for $\text{C}_{21}\text{H}_{31}\text{N}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 375.2101, found: 375.2100. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (98:2 hexane:*i*-PrOH, 1.5 mL/min, 254 nm, 25 °C); t_r (minor) = 3.0, t_r (minor) = 3.3 min, 82% ee.

Minor diastereomer: R_f 0.20 (20% EtOAc/petroleum ether); $[\alpha]_D^{22} +25.6$ (c 0.78, CHCl_3); IR (CHCl_3) 2932, 2856, 1712 ($\text{C}=\text{O}$), 1501, 1453, 1439, 1368, 1242, 1168, 882 cm^{-1} ; ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{CO}$) δ 8.00 (1H, d, $J = 7.9$ Hz, ArH), 7.93 (1H, d, $J = 8.1$ Hz, ArH), 7.51-7.46 (1H, m, ArH), 7.42-7.36 (1H, m, ArH), 5.91 (1H, d, $J = 10.2$ Hz, NH), 3.92 (1H, dtt, $J = 16.0, 13.1, 8.0$ Hz, CHN), 3.60 (1H, app quin, $J = 7.0$ Hz, CHCH₃), 1.93-1.84 (1H, m CH₂), 1.72-1.63 (3H, m, CH₂), 1.60-1.56 (1H, m, CH₂), 1.41-1.39 (4H, m, CH and CHCH₃), 1.36 (9H, s, C(CH₃)₃), 1.19-1.04 (5H, m, CH₂); ^{13}C NMR (125.8 MHz, $(\text{CD}_3)_2\text{CO}$) δ 175.9 (C), 157.0 (C), 154.1 (C), 135.9 (C), 126.6 (CH), 125.6 (CH), 123.5 (CH), 122.6 (CH), 78.5 (C), 60.3 (CH), 41.7 (CH), 40.8 (CH), 31.5 (CH₂), 28.6 ($3 \times \text{CH}_3$), 28.1 (CH₂), 27.1 (CH₂), 26.9 (CH₂), 26.8 (CH₂), 17.5 (CH₃). HRMS (ESI) Exact mass calcd for $\text{C}_{21}\text{H}_{31}\text{N}_2\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$: 375.2101, found: 375.2099.

Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98:2 hexane:*i*-PrOH, 1.5 mL/min, 254 nm, 25 °C): t_r (major) = 17.4 min, t_r (minor) = 28.6 min, 75% ee.

Deprotection of 231a

(1*R*,2*S*)-1-(Naphthalen-2-yl)-2-(quinolin-2-yl)propan-1-amine (222)



TMSCl (0.14 mL, 1.12 mmol) was added carefully to MeOH (1.1 mL) and the resulting solution was stirred for 10 min before *N*-Boc-protected amine **221a** (46 mg, 0.11 mmol) was added. The solution was heated at 50 °C for 30 min and cooled to room temperature. The mixture was diluted with EtOAc (5 mL), washed with 1:1 saturated aqueous NaHCO₃ solution/brine (2 × 5 mL) and brine (5 mL), dried (MgSO₄), and concentrated *in vacuo* to give the amine **222** (31 mg, 90%) as a white solid. *R*_f 0.50 (30% acetone/petroleum ether with 1% Et₃N); m.p. 134-136 °C (EtOAc/petroleum ether); $[\alpha]_{\text{D}}^{19} +14.0$ (*c* 0.72, CHCl₃); IR (CHCl₃) 3060 (NH), 2969, 2934, 1620, 1601, 1562, 1505, 1428, 1374, 831 cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 8.29 (1H, d, *J* = 8.4 Hz, ArH), 8.10 (1H, d, *J* = 8.4 Hz, ArH), 7.95-7.83 (5H, m, ArH), 7.77 (1H, t, *J* = 7.6 Hz, ArH), 7.64-7.55 (2H, m, ArH), 7.56-7.44 (3H, m, ArH), 4.55 (1H, br s, CHN), 3.56-3.43 (1H, m, CHCH₃), 1.16 (3H, d, *J* = 6.8 Hz, CHCH₃); ¹³C NMR (125.8 MHz, CD₃OD) δ 166.1 (C), 148.9 (C), 142.1 (C), 138.6 (CH), 134.9 (C), 134.5 (C), 130.9 (CH), 129.4 (CH), 129.2 (CH), 129.0 (CH), 128.9 (CH), 128.7 (CH), 127.7 (CH), 127.4 (CH), 127.2 (CH), 126.9 (CH), 126.1 (CH), 122.5 (CH), 62.1 (CH), 51.0 (CH), 19.3 (CH₃), peak for one carbon could not be determined unambiguously due to possible overlapping signals; HRMS (ESI) Exact mass calculated for C₂₂H₂₁N₂ [M+H]⁺: 313.1699, found: 313.1698. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane:*i*-PrOH, 1.5 mL/min, 230 nm, 25 °C); *t*_r (major) = 24.4, *t*_r (minor) = 28.0 min; 86% ee.

4.3 X-Ray Crystallography Data

The X-ray crystallography data can be obtained free of charge from The Cambridge Crystallographic Data Centre (CCDC) *via* www.ccdc.cam.ac.uk/data_request/cif.

Table 4.01: X-Ray Crystallography Data

Compound Number	CCDC Number
221f	1019731
231d	1019733
231k	1019735
231r	1019734
231t	1019732
231u	1019732

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